Copper(I)-Assisted Mild and Convenient Synthesis of New Se−N Heterocycles: Access to a Promising Class of GPx Mimics

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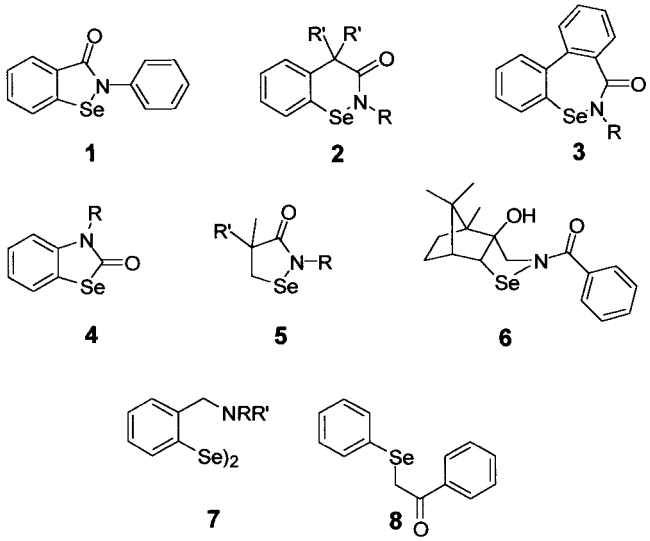
Benzisoselenazolines **15** and benzisoselenazines **21**, designed as low molecular weight mimics of glutathione peroxidases, were synthesized for the first time. Starting from amines **13** and **14**, a smooth introduction of selenium in nonactivated aryl bromides using KSeCN in the presence of CuI was developed. An equimolar quantity of CuI and the presence of Et_3N as a base are necessary to achieve a complete conversion of the starting material. The reaction is feasible in various solvents such as DMF, acetonitrile, and THF. The desired new Se−N heterocycles **15** and **21** were isolated under optimized conditions in yields of 82 and 68%, respectively. Experiments have been conducted with various copper(I) and copper(II) salts, a chloroamine **17**, an aryl bromide **18**, and an N-acylated amine **19** to show the scope and the limitations of this method. The previously unknown sulfur analogues **20** and **22** have been synthesized in moderate yields using a slightly modified procedure. Finally, a mechanistic scheme has been proposed to discuss some interesting findings, which were obtained during the optimization process of this new introduction of selenium.

Introduction[1]

Glutathione peroxidases (GPx's), discovered in 1973 by Flohé et al.,[2] are selenium-containing enzymes that, at the expense of glutathione (GSH), reduce hydrogen peroxide and organic hydroperoxides to alcohols and water (eq 1).

$$ROOH + 2\,GSH \xrightarrow{GPx} ROH + GSSG + H_2O \quad (1)$$

As a key enzyme in the antioxidant defense system,[3] its biological role does not only comprise the detoxification by reducing an overproduction of hydroperoxides, but also the regulation of intracellular signaling pathways[4] and enzyme activities, such as that of 5-lipoxygenase.[5] The pharmacological potential of increased intracellular GPx-activity was illustrated by the microinjection of purified enzyme, which engendered an increase in the survival of cells exposed to reactive oxygen species (ROS), generated by hyperoxia or redox cyclers.[6] To circumvent the intrinsic difficulties connected with the use of an enzyme as a drug, a number of selenium-based, small-molecular weight mimics[7] of GPx have been studied in the past. To those belong the well-known ebselen (**1**)[8,9] and its homologues **2**[10] and **3**,[11] benzisoselenazolinones **4**,[12] peptide- or campher-derived selenenamides **5**[13] and **6**,[14] diselenides **7**,[15] and phenylselenoacetophenones **8**.[16]



In this context, we were interested in the design[17] and synthesis of benzisoselenazolines **9** and benzisoselen-

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(1) Part of this work has been presented as a poster communication at the 213th ACS National Meeting, San Francisco, 1997, and as an oral communication at the VIIth International Conference on the Chemistry of Selenium and Tellurium, Vaalsbroek Castle, 1997.

(2) Flohé, L.; Gunzler, W. A.; Schock, H. H. *FEBS Lett.* **1973**, *32*, 132.

(3) Raes, M.; Michiels, C.; Remacle, J. *Free Radical Biol. Med.* **1987**, *3*, 3.

(4) Krebz-Remy, C.; Mehlen, P.; Mirault, M. E.; Arrigo, A. P. *J. Cell Biol.* **1996**, *133*, 1083.

(5) Weitzel, F.; Wendel, A. J. *Biol. Chem.* **1993**, *268*, 6288.

(6) (a) Michiels, C.; Remacle, J. *Biochim. Biophys. Acta* **1988**, *967*, 341. (b) Michiels, C.; Toussaint, O.; Remacle, J. *J. Cell. Physio.* **1990**, *144*, 295.

(7) (a) Macromolecular GPx-mimics are described in: Wu, Z.-P.; Hilvert, D. *J. Am. Chem. Soc.* **1990**, *112*, 5647; Peterson, E. B.; Hilvert, D. *Tetrahedron* **1997**, *53*, 12311 and Liu, J. Q.; Luo, G. M.; Gao, S. J.; Zhang, K.; Chen, X. F.; Shen, J. C. *Chemical Communications* **1999**, 199. (b) For tellurium-based mimics see: Engman, L.; Stern, D.; Cotgreave, I. A.; Andersson, C. M. *J. Am. Chem. Soc.* **1992**, *114*, 9737; Engman, L.; Stern, D.; Pelcman, M.; Andersson, C. M. *J. Org. Chem.* **1994**, *59*, 1973; Vessman, K.; Ekstroem, M.; Berglund, M.; Andersson, C.; Engman, L. *J. Org. Chem.* **1995**, *60*, 4461; Kanda, T.; Engman, L.; Cotgreave, I. A.; Powis, G. *J. Org. Chem.* **1999**, *64*, 8161. (c) An organometallic GPx-like compound is described in: Spector, A.; Wang, G.-M.; Wang, R.-R. *Proc. Natl. Acad. Sci. U.S.A.* **1993**, *90*, 7485.

(8) For a review see: Sies, H. *Free Radical Biol. Med.* **1993**, *14*, 313.

(9) A sulfonamide-based analogue of Ebselen is described in: Mhizha, S. *Tetrahedron* **1997**, *53*, 17751.

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azines **10** and their use as pharmacological agents.[18] Such cyclic selenenamides without a carbonyl function on the nitrogen have not been described previously. Moreover, it was proposed[10,11] that the C=O function in compounds such as **1**−**3** is necessary to stabilize the selenenamide-structure. Herein we describe the first synthesis of benzisoselenazolines **9** and benzisoselenazines **10** and the development of a convenient and industrializable access to these new selenium−nitrogen heterocycles.

n = 0: **9**
n = 1: **10**

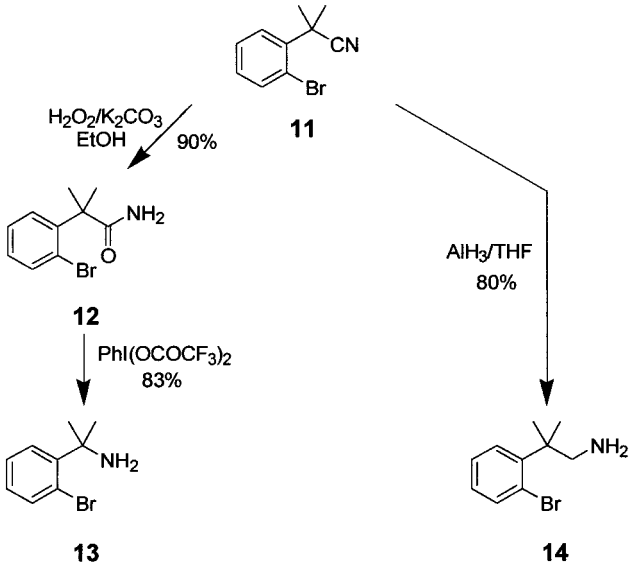
Results and Discussion

The *o*-bromophenylalkylamines **13** and **14** were chosen as the starting material for the synthesis of the new heterocycles. Starting from 2′-bromophenyl-2-methylpropionitrile (**11**),[19] they are easily accessible on a multigram scale in one and two steps, respectively, according to Scheme 1.

We first focused on the synthesis of the five-membered heterocycle **15** which should be accessible by the introduction of selenium in the ortho-position of **13** to yield compounds of type **16**, followed by cyclization (see Scheme 2).

Usually, selenenamides are obtained starting from selenenic acids **16a**, selenyl chlorides **16b** or selenyl bromides **16c** and, in some rare examples, from selenocyanates **16d**.[20,21] From an industrial viewpoint, the introduction of selenium in the form of ≪ SeCN ≫ to provide **16d** seemed most appealing to us, as KSeCN is a commercially available and an easy-to-handle selenium reagent.

Scheme 1



Scheme 2

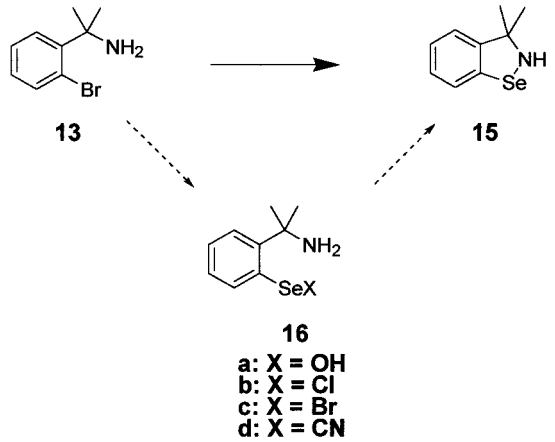


Table 1. Reaction of 13 with KSeCN in DMF[a]

entry	equiv of KSeCN	equiv of CuI	equiv of Et_3N	conversion of **13**[b] (%)	yield of **15**[c] (%)
1	1			<5	<5[d]
2	1	0.2		n.d.	15
3	3 or 5	0.2		20	n.d.
4	1	1		50	40
5	1.2	1	3	89	82

[a] 1 mmol **13**/5 mL DMF at room temperature/24 h; see General Procedure 1. [b] Determined by ^1H NMR of the reaction mixture; see General Procedure 1. [c] Isolated yield. [d] The same result is obtained after 24 h/110 °C.

First, we examined the synthesis of the selenocyanate **16d** by direct nucleophilic substitution. Treatment of **13** with KSeCN in DMF for 24 h, either at room temperature or 110 °C, did not provide any new products (Table 1, entry 1).[22,23] As copper(I) iodide is commonly used to catalyze the substitution of nonactivated aryl bromides or iodides,[24,25] we repeated the reaction of the amine **13**

(10) Jacquemin, P. V.; Christiaens, L. E.; Renson, M. J.; Evers, M. J.; Dereu, N. *Tetrahedron Lett.* **1992**, *33*, 3863.
(11) Mohsine, A.; Christiaens, L. *Heterocycles* **1996**, *43*, 2567.
(12) Galet, V.; Bernier, J.; Henichart, J.; Lesieur, D.; Abadie, C.; Rochette, L.; Lindenbaum, A.; Chalas, J.; Renaud de la Faverie, J.; Pfeiffer, B.; Renard, P. *J. Med. Chem.* **1994**, *37*, 2903.
(13) (a) Reich, H. J.; Japserse, C. P. *J. Am. Chem. Soc.* **1987**, *109*, 5549. (b) Chan, P., Cotelle, P.; Bernier, J. L., Hénichart, J. P. *Bioorg. Med. Chem. Lett.* **1991**, *1*, 277. (c) Cotelle, P.; Chan, P.; Cotelle, N.; Bernier, J. L.; Henichart, J. P. *J. Chim. Phys.-Chim. Biol.* **1992**, *89*, 191.
(14) Back, T. G.; Dyck, B. P. *J. Am. Chem. Soc.* **1997**, *119*, 2079.
(15) (a) Wilson, S. R.; Zucker, P. A.; Huang, R.-R. C.; Spector, A. *J. Am. Chem. Soc.* **1989**, *111*, 5936. (b) Iwaoka, M.; Tomoda, S. *J. Am. Chem. Soc.* **1994**, *116*, 2557.
(16) (a) Cotgreave, I. A.; Moldeus, P.; Brattsand, R.; Hallberg, A.; Andersson, C. M.; Engman, L. *Biochem. Pharmacol.* **1992**, *43*, 793. (b) Engman, L.; Andersson, C.; Morgenstern, R.; Cotgreave, I. A.; Andersson, C. M.; Hallberg, A. *Tetrahedron* **1994**, *50*, 2929.
(17) For a detailed discussion of the rationale of design of the new compounds see: Chaudière, J.; Yadan, J.-C.; Erdelmeier, I.; Tailhan-Lomont, C.; Moutet, M. In *Oxidative Processes and Antioxidants*; Paoletti, R., et al., Eds.; Raven Press Ltd.: New York, 1994; p 165.
(18) Erdelmeier, I.; Chaudière, J.; Moutet, M.; Yadan, J. C. PCT Application WO 9527706.
(19) Parham, W. E.; Jones, L. D. *J. Org. Chem.* **1976**, *41*, 1187.
(20) (a) Paulmier C. *Selenium Reagents and Intermediates In Organic Synthesis*; Pergamon Press: Oxford, New York, 1986. (b) Liotta, D. *Organoselenium Chemistry;* John Wiley: New York, 1987. (c) Kirsch, G.; Christiaens, L. In *The Chemistry of Organic Selenium and Tellurium Compounds*; Patai, S., Ed.; John Wiley: New York, 1987; Vol. 2, pp 424−428.
(21) For a radical-based synthetic approach to Ebselen and analogues see: Fong, M. C.; Schiesser, C. H. *J. Org. Chem.* **1997**, *62*, 3103.
(22) The nucleophilic selenium reagents NaHSe and Na_2Se did also not react with amine **13** under the following conditions: Na_2Se: 18 h rt or 110 °C/DMF.; NaHSe: H_2O/toluene/PTC(tetrabutylammonium bromide), 18 h rt or 18 h 100 °C.
(23) A photoinduced substitution of chlorine by the selenocyanate ion is reported for donor-substituted aryl chlorides in Frolov, A. N.; Smirnov, E. V.; Kul'bitskaya, O. V.; El'tsov, A. V. *Zh. Org. Khim.* **1980**, 2302.

Table 2. Influence of the Metal Salt on the Reaction of 13 with KSeCN[a]

entry	MX	equiv of Et_3N	conversion of **13** (%) 24 h	conversion of **13** (%) 40 h	yield of **15** (%) 40 h
1	CuI	3	89	100	84
2	CuBr	3	78	95	82
3	CuCl	3	72	91	80
4	CuCN	3	40	56	40
5	$CuBr_2$		<5	<5	<5
6	$CuBr_2$	3	n.d.	97	82
7	$Pd(PPh_3)_4$	3	<5	<5	<5
8	$Pd_2(dba)_3$	3	<5	<5	<5

[a] 1 mmol **13**/5 mL DMF/rt/24 h; product distribution determined by ^{1}H NMR of the reaction mixture; see General Procedure 2.

in DMF, but now in the presence of 20 mol % CuI. At rt, we observed slow formation of a new and relatively nonpolar product in poor yield (after 24 h) which we isolated and characterized. Much to our surprise, the crystalline compound proved not to be the selenocyanate **16d**, but the desired heterocycle **15** (15%, Table 1, entry 2). Interestingly, **15** was stable against air oxidation and decomposition as illustrated by a shelf life of several months at room temperature and reversible melting without any deposition of red selenium.[26]

Further experiments showed that the conversion of amine **13** stopped at about 20%, even in the presence of 3 or 5 equiv of KSeCN (Table 1, entry 3). An equimolar amount of CuI was necessary to obtain **15** in better yield (40%, Table 1, entry 4), but the ^{1}H NMR spectra of the crude homogeneous reaction mixture (after 24 h at room temperature) revealed that the conversion of **13** did not progress further than 50%. As formally one molecule of HBr is formed upon the reaction of one molecule of **13**, we supposed that protonation of the starting material precluded its complete conversion. This hypothesis could be confirmed. At rt in the presence of 3 equiv of triethylamine as a base, a smooth and high conversion of **13** to **15** could be observed. This eventually allowed the isolation of **15** in good yields (82%, Table 1, entry 5).

The reaction is general for copper(I) salts with differences in the time range for conversion of **13** (Table 2, entries 1−4). In the absence of Et_3N (Table 2, entry 5), copper(II) salts are not efficient in this reaction.[27] Nevertheless, they can also be used in the presence of Et_3N, as it is known[28] to reduce Cu(II) to Cu(I) in situ (Table 2, entry 6).

It is noteworthy that we did not observe any conversion of **13** in the presence of $Pd(PPh_3)_4$ or Pd_2dba_3 (Table 2, entries 7−8).

Interestingly, the copper(I)-assisted synthesis of **15** using KSeCN is feasible in a wide variety of organic solvents (see Table 3).

For this study, we conducted the reaction under standard conditions and analyzed the crude product

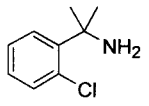
Table 3. Copper(I)-assisted Reaction of 13 with KSeCN in Different Solvents[a]

entry	solvent	**13** (%)	"X" (%)	**15** (%)
1	DMF[b]	6	2	92
2	DMF + 1% H_2O[b]	6	2	92
3	CH_3CN[c]	2	2	96
4	THF[c]	8	2	90
5	THF + 1% H_2O[c]	11	7	82
6	EtOH[c]	39	6	55
7	EtOH + 1% H_2O[c]	43	8	49
8	CH_2Cl_2[c]	13	24	63
9	toluene[c]	67	4	29

[a] 1 mmol **13**/5 mL solvent/rt/24 h; product distribution determined by ^{1}H NMR of the crude product; see General Procedure 3. [b] Homogeneous reaction mixture. [c] Heterogeneous reaction mixture.

obtained after 24 h by ^{1}H NMR analysis using the very distinct protons of the dimethyl group as a probe. In all the examples, besides **15** and starting material **13**, signals of an unknown polar byproduct were observed, usually in small amounts except for the reaction in CH_2Cl_2. The Se−N-heterocycle **15** was formed in good yields not only in dry DMF, acetonitrile, and THF (Table 3, entries 1, 3−4) but also in "wet" solvents (Table 3, entries 2 and 5) where 1% of water has been added. In the majority of these examples (entries 3 to 9) the reaction mixture was heterogeneous. Therefore, homogeneity is apparently not a prerequisite for a smooth reaction.

To explore the scope of this mild introduction of selenium, we treated the structurally related aryl chloride **17** and aryl bromides **18** and **19** under the conditions optimized for the preparation of **15** (1.2 KSeCN, DMF, 3 Et_3N, 24 h rt). After 24 h at room temperature, no conversion of **17**,[29] **18**, or **19** could be detected, and the starting material was recovered unchanged. These results suggest that the presence of a basic nearby amino group allows for the very mild conditions of the substitution of bromine in the nonactivated aryl bromide **13**. These are significantly milder in comparison to the conditions reported in the literature for copper(I)-catalyzed introduction of SeCN in aryl iodides (HMPA/100 °C[24]).



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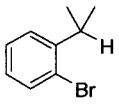

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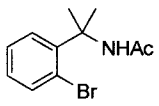

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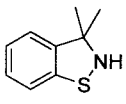

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Interestingly, the previously unknown sulfur analogue of **15**, the thiazoline **20**, could be obtained in moderate yields using a slightly modified protocol. Reaction of **13** with 1.2 equiv of KSCN in the presence of CuI and triethylamine in THF/DMF at 80 °C for 2 h afforded **20** in 22% yield (at room temperature, this reaction was sluggish and slow).

(24) (a) Suzuki, H.; Shinoda, M. *Synthesis* **1977**, 640. (b) Suzuki, H.; Miyoshi, K.; Shinoda, M. *Bull. Chem. Soc. Jpn.* **1980**, *53*, 1765.

(25) Lindley, J. *Tetrahedron* **1984**, *40*, 1433.

(26) **15** is also surprisingly stable against hydrolysis as shown by 96% recovery of pure product after refluxing for 24 h in methanol in the presence of 10 eq. of NaOH.

(27) For the photoinduced Cu(II)-catalyzed substitution of arlhalogenides by selenocyanate, see, for example: (a) Smirnov, E. V.; Frolov, A. N.; El'tsov, A. V. *Zh. Org. Khim.* **1975**, *11*, 1254. (b) Nefedov, V. A.; Tarygina, L. K.; Kryuchkova, L. V.; Ryabokobylko, Y. S. *Zh. Org. Khim.* **1981**, *17*, 570. (c) Nefedov, V. A. *Zh. Obshch. Khim.* **1981**, *38*, 2191.

(28) (a) Yoke, J. T.; Weiss, J. P.; Tollin, G. *Inorg. Chem.* **1963**, *2*, 1210. (b) Weiss, J. P.; Tollin, G.; Yoke, J. T. *Inorg. Chem.* **1964**, *3*, 1344.

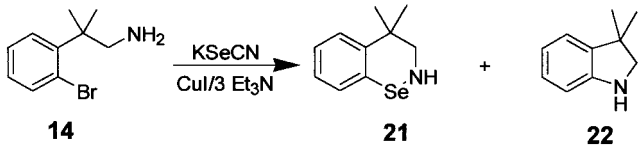
(29) Only at slightly elevated temperature (60 °C) was compound **15** formed in low yield (7% after 24 h) accompanied by large amounts of starting compound **17** (87%) and an unknown side product (6%).

Table 4. Copper(I)-Assisted Reaction of 14 with KSeCN[a]

entry	equiv of KSeCN	conversion of **14** (%)	**21**:**22**
1	1	quant.	68:32[b]
2	2	quant.	75:25[c]
3	3	89	80:20
4	5	78	80:20
5	2[d]	97	75:25[e]
6	2[f]	87	77:23[e]

[a] 1 mmol **14**/5 mL DMF/rt/24 h; product distribution determined by ^{1}H NMR of the crude product; see General Procedure 4. [b] Isolated yield of **21**: 51%. [c] Isolated yield of **21**: 68%. [d] In dry CH_3CN. [e] Heterogeneous reaction mixture. [f] In dry THF.

Scheme 3



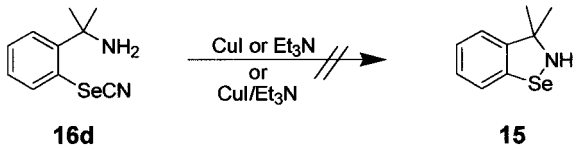
14 **21** **22**

Encouraged by the successful and convenient synthesis of the selenazoline **15** using the copper(I)-assisted introduction of selenium and its surprising stability, we attempted a comparable synthesis of selenazine **21**. The reaction of amine **14** with one equivalent of KSeCN in the presence of CuI and Et_3N proceeded within 24 h at room temperature with complete conversion of the starting material. Two new products with a very close polarity were formed in a ratio of 68:32 in the crude mixture (Table 4, entry 1). After separation and complete characterization, the major product was identified as the desired heterocycle **21** (51% isolated yield),[30] whereas the byproduct proved to be the known 3,3-dimethylindolin **22**.[31] Varying the amount of KSeCN from 1 to 5 equiv under conditions otherwise identical, we observed a reduction in the conversion of **14** (see Table 4). Moreover, the ratio of selenazine to indolin could first be raised from 68:32 (Table 4, entry 1) to 80:20 (Table 4, entry 3) in the crude reaction mixture, when using 3 equiv of KSeCN, but remained unchanged upon reaction in the presence of 5 KSeCN (Table 4, entry 4).

As a compromise between reaction time and selectivity for the desired product **21**, we chose the following optimal protocol for the conversion of **14**: 2 equiv of KSeCN/1 CuI/3 Et_3N for 24 h at room temperature, which allowed us to isolate **21** in 68% yield after chromatography. Applying these conditions without further modifications on a kg scale, **21** could be obtained analytically pure (45%) after a single recrystallization of the crude product from *n*-hexane.

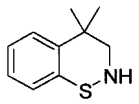
As shown above for the synthesis of **15**, compound **21** can also be obtained in good yield in acetonitrile or THF (Table 4, entries 5−6). The analysis of the crude reaction product by ^{1}H NMR analysis revealed that the ratio of selenazine **21** to indolin **22** was about 75:25 under such conditions, and hence similar to the result obtained in DMF.

Scheme 4



16d **15**

Finally, the analogous treatment of the amine **14** with KSCN instead of KSeCN in THF/DMF for 2 h at 80 °C under conditions otherwise identical resulted in a mixture of indolin **22** and the new thiazine **23** (30%).[32]



23

Although the detailed mechanism has not been clarified, the following observations seem to be noteworthy: (i) the very smooth reaction conditions (24 h rt) for the insertion of "Se" in a nonactivated aryl−Br bond, (ii) the concurrent formation of indolin **22** upon the reaction of amine **14**, (iii) the reduced conversion when using an excess of KSeCN, (iv) the ceiling of the ratio of **21** to **22** (80:20) when varying the equivalents of KSeCN, and (v) the almost constant ratio of the obtained products in various solvents. These observations would be consistent with the intermediate formation of a copper complex, in which the neighboring amino function could first precomplex the copper(I), thereby facilitating the subsequent activation of the nearby C−Br bond for substitution. As discussed already, we supposed that selenocyanate **16d** would be formed, which could then cyclize to yield the desired heterocyclic compound **15** (see Scheme 2). Incidentally, we discovered during the scale-up of the process that selenazoline **15** was rapidly converted into a new, relatively unstable compound, when treated with KCN[33] in acetonitrile. According to the spectral data, we assigned the selenocyanate structure **16d** to this new product. Much to our surprise, this compound did not cyclize as supposed to heterocycle **15** under the conditions of its synthesis, for instance, in the presence of CuI or Et_3N. *Therefore, these findings seem to preclude the formation of selenocyanate **16d** as an intermediate to **15**.* We now tentatively propose a copper complex, such as **24**,[25] as the intermediate, which would then cyclize—potentially via a second intermediate—to give **15** and **21**, respectively. The formation of indolin **22**, the amelioration of the ratio of **21** to **22** by using more than 1 equiv of KSeCN, and the constant ratio with more than 3 equiv of KSeCN could then tentatively be explained by an intramolecular competition for cyclization of the amine function and the SeCN-ion and the occupation of all free coordination places about the copper-core in **24** when using selenocyanate in excess (≥3 equiv).

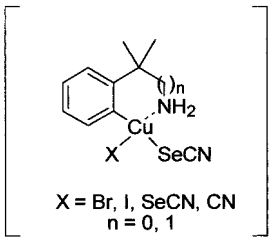
In conclusion, we have developed a convenient access to the hitherto unknown[1,18] selenium-containing heterocycles **15** and **21** by a copper(I)-assisted introduction of selenium and have studied its scope and limitations. These very stable, crystalline compounds **15** and **21**,

(30) This new crystalline selenium-containing compound is almost odorless and has a shelf life of several months at room temperature, a reversible melting without decomposition, and about the same stability as the five-membered heterocycle **15**. These findings seem to indicate that the stabilization of the Se−N bond by an adjacent carbonyl function, as proposed for Ebselen (**1**), and compounds **2** and **3**, is not necessarily required to obtain stable selenenamides.

(31) This latter product was also the major compound formed when running the reaction in the absence of KSeCN (data not shown).

(32) At room temperature, the reaction was very sluggish and slow.

(33) The treatment of the reaction mixture with an aqueous solution of 3 equivalents of NaCN or KCN was applied first during a multigram-synthesis of **21**, where the complexation of the copper(I) salts in a soluble form facilitated the workup considerably.



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which we synthesized as potential mimics of glutathione peroxidases, exhibited new and promising biological activites[34] as well as other substituted compounds which were synthesized in analogy.[18,35] One of them, compound **21**, showed higher GPx-activity than Ebselen and potent inhibition of TNF-α induced endothelial alterations.[36] According to the process described herein, it was prepared on a kilogram scale, and it is actually in clinical development as a drug candidate for the treatment of ulcerative colitis.

Experimental Section

Unless stated otherwise, solvents were dried by distillation under N_2 from sodium benzophenone ketyl (THF, Et_2O) or CaH_2 (CH_2Cl_2, CH_3CN). All reagents were of commercial quality and were used without further purifications. **Caution!** KSeCN is highly toxic and should be handled with extreme care, using efficient fume hoods and appropriate personal protection. All reactions were performed in oven-dried glassware under N_2. Flash chromatography was carried out on silica gel 60 (230−400 mesh) from Merck. Analytical thin-layer chromatography (TLC) was performed on precoated silica gel aluminum plates (Macherey Nagel) and visualized with ultraviolet light (254 nm).^{1}H NMR and ^{13}C NMR spectra were recorded at 200 MHz and 50 MHz, respectively, in $CDCl_3$ unless otherwise stated. ^{77}Se−NMR spectra have been recorded at 47.7 MHz and 95 MHz. Melting points were determined on a Gallenkamp apparatus and were uncorrected. Standard mass spectra and acurate mass measurements were recorded on a Nermag R10−10B instrument. The ionization methods used were desorption chemical ionization (CI) and electron impact ionization (EI). Combustion analyses were performed by Laboratoires Wolff, Clichy, France. The following compounds were prepared by known standard procedures: 2′-bromophenyl-2-methylpropio-nitrile (**11**)[19] and NaHSe.[37]

2-Bromo-α,α-dimethylbenzeneacetamide (12). To a stirred solution of **11** (6.7 g, 30 mmol) in EtOH (70 mL) was added first a saturated aqueous solution of K_2CO_3 (70 mL), and then, with caution,[38] an aqueous solution of H_2O_2 (50%, 2 × 70 mL) at 10−15 °C. The reaction mixture was stirred for 14 h at room temperature,[39] and then it was extracted with CH_2Cl_2 (1 × 200 mL, 1 × 100 mL). The combined organic extracts were washed with water (3 × 200 mL), dried ($MgSO_4$), and concentrated to provide **12** as a colorless, highly viscous oil (6.56 g, 90% after Kugelrohr distillation,[40] 0.1 mbar, 200−220 °C) ^{1}H NMR (200 MHz) δ 1.65 (s, 6H), 5.20 (br s, 1H), 5.40 (br s, 1H), 7.13 (m, 1H), 7.32 (m, 1H), 7.48 (m, 1H), 7.60 (m, 1H); ^{13}C NMR (50 MHz) δ 26.3, 26.6, 48.3, 124.5, 128.0, 129.1, 135.2, 136.4, 143.3. MS (CI) *m/z* 244/242 (100, MH^+); HRMS calcd for $C_{10}H_{13}{}^{79}BrNO$ (MH^+) 242.0181, found *m/z* 242.0175; calcd for $C_{10}H_{13}{}^{81}BrNO$ 244.0161, found *m/z* 244.0160.

2-Bromo-α,α-dimethylbenzenemethanamine (13). Bis-(trifluoroacetoxy)iodobenzene[41] (10.88 g, 25.3 mmol) was added in one portion to a solution of **12** (6.12 g, 25.3 mmol) in acetonitrile (30 mL) and water (30 mL). The reaction mixture was stirred at room temperature. After 24 h, water (450 mL) was added, and stirring was continued for 30 min. The mixture was extracted with *tert*-butyl methyl ether (4 × 150 mL). The pH of the aqueous phase was adjusted to 12−14 by the addition of 10% aqueous NaOH at 10 °C. Extraction with CH_2Cl_2 (3 × 150 mL), drying ($MgSO_4$), and evaporation of the solvents afforded **13** as a colorless oil (4.49 g, 83% after Kugelrohr distillation,[40] 0.1 mbar, 60−70 °C): ^{1}H NMR (200 MHz) δ 1.65 (s, 6H), 2.16 (br s, 2H), 7.05 (m, 1H), 7.25 (m, 1H), 7.57 (m, 2H); ^{13}C NMR (50 MHz) δ 30.7, 54.2, 122.2, 127.8, 127.9, 128.6, 136.1, 147.8; MS (CI) *m/z* 216/214 (100, MH^+); HRMS calcd for $C_9H_{13}{}^{79}BrN$ (MH^+) 214.0231, found *m/z* 214.0229; calcd for $C_9H_{13}{}^{81}BrN$ 216.0211, found *m/z* 216.0220.

2-Bromo-β,β-dimethylbenzeneethanamine (14). A solution of AlH_3 in THF was prepared by adding with caution a solution of concentrated H_2SO_4 (12.6 g, 0.12 mol) in THF (60 mL) to a suspension of LAH (8.97 g, 0.236 mol) in THF (180 mL) at 0−5 °C, followed by stirring for 2 h at room temperature. Nitrile **11** (38.7 g, 0.173 mol) in THF (100 mL) was then added, and the mixture was refluxed for 3 h. After cooling to 0 °C, an aqueous solution of H_2SO_4 (14%, 400 mL) was added dropwise, and the mixture was stirred at room temperature for 14 h. After a second addition of an aqueous solution of H_2SO_4 (8%, 130 mL), THF was evaporated under reduced pressure (200 mbar). The aqueous phase was washed with TBME (2 × 75 mL), and the pH was adjusted to 13 with a 35% aqueous solution of NaOH (150 mL) at 5 °C. Extraction with *tert*-butyl methyl ether or CH_2Cl_2 (5 × 50 mL), washing of the combined organic phases with water (3 × 40 mL), drying (Na_2SO_4), filtration over a pad of Celite, and concentration afforded **14** as a colorless oil (31.55 g, 80%): ^{1}H NMR (200 MHz) δ 1.40 (br s, 2H), 1.44 (s, 6H), 3.19 (s, 2H), 7.03 (td, 1H, J = 8.0, 8.0, 2.0 Hz), 7.24 (td, 1H, J = 8.0, 8.0, 1.5 Hz), 7.38 (dd, 1H, J = 8.0, 2.0 Hz), 7.57 (dd, 1H, J = 8.0, 8.0, 1.5 Hz); ^{13}C NMR (50 MHz) δ 26.6, 42.4, 50.7, 122.7, 127.9, 128.5, 130.6, 136.4, 144.8. MS (CI) *m/z* 230/228 (100, MH^+), 148 (30); HRMS calcd for $C_{10}H_{15}{}^{79}BrN$ (MH^+) 228.0388, found *m/z* 228.0389; calcd for $C_{10}H_{15}{}^{81}BrN$ 230.0368, found *m/z* 230.0382.

2-Chloro-α,α-dimethylbenzeneacetamide. 2-Chloro-α,α-dimethylbenzeneacetamide was prepared from 2′-chlorophenyl-2-methylpropionitrile according to the procedure described for **12**: yield 83% after distillation[40] (Kugelrohr, 0.1 mbar, 150−170 °C); ^{1}H NMR (200 MHz) δ 1.59 (s, 6H), 5.24 (br s, 1H), 6.03 (br s, 1H), 7.10−7.50 (m, 4H); ^{13}C NMR (50 MHz) δ 26.1, 47.0, 127.2, 127.6, 128.7, 131.4, 134.5, 142.0, 179.8. MS (CI) *m/z* (%) 200/198 (35/100, MH^+); HRMS calcd for $C_{10}H_{13}{}^{35}ClNO$ (MH^+) 198.0686, found *m/z* 198.0680; calcd for $C_{10}H_{13}{}^{37}ClNO$ 200.0659, found *m/z* 200.0654.

2-Chloro-α,α-dimethylbenzenemethanamine (17). Compound **17** was prepared from 2-chloro-α,α-dimethyl-benzeneacetamide according to the procedure described for **13**: yield 71%; ^{1}H NMR (200 MHz) δ 1.61 (s, 6H), 1.99 (br s, 2H), 7.17 (m, 2H), 7.34 (m, 1H), 7.54 (m, 1H); ^{13}C NMR (50 MHz) δ 30.0, 52.9, 126.9, 127.9, 131.9, 132.7, 145.9; MS (CI) *m/z* (%) 172/170 (35/100, MH^+); HRMS calcd for $C_9H_{13}{}^{35}ClN$ (MH^+) 170.0737, found *m/z* 170.0735; calcd for $C_9H_{13}{}^{37}ClN$ 172.0708, found *m/z* 172.0679.

(34) (a) Chaudiere, J.; Moutet, M.; D'Alessio, P. *C. R. Seances Soc. Biol. Ses Fil.* **1995**, *189*, 861. (b) D'Alessio, P.; Moutet, M.; Chaudière, J. *C. R. Séances Soc. Biol.* **1996**, *190*, 289. (c) D'Alessio, P.; Moutet, M.; Coudrier, E.; Darquenne, S.; Chaudière, J. *Free Radical. Biol. Med.* **1998**, *24*, 979. (d) D'Alessio, P.; Marsac, C.; Moutet, M.; Chaudière, J. In *Oxidative Stress in Cancer, AIDS and Neurodegenerative Diseases*; Montagnier, L., Olivier, R., Pasquier, C., Eds.; Marcel Dekker: New York, 1998; pp 313−321.

(35) Erdelmeier, I.; Tailhan-Lomont, C.; Moutet, M.; Chaudière, J.; Yadan, J.-C. PCT Application WO9829417.

(36) Moutet, M.; d'Alessio, P.; Malette, P.; Devaux, V.; Chaudière, J. *Free Radical Biol. Med.* **1998**, *25*, 270.

(37) (a) Klayman, D. L.; Griffin, T. S. *J. Am. Chem. Soc.* **1973**, *95*, 197. (b) Spyer, L.; Mlochowski, J. *Synthesis* **1984**, 439.

(38) We observed in one of a series of experiments an exothermic reaction progress, and this about 1 h after the addition of H_2O_2.

(39) A TLC control (SiO_2, EtOAc, R_f (**11**) = 0.95, R_f (**12**) = 0.3) is necessary to confirm complete hydrolysis of **11**. In some experiments the reaction was not complete at this moment, and 70 mL of aqueous H_2O_2 have been added again to the mixture and the reaction treated after a total of 24 h.

(40) The crude product can be directly used without distillation in the next step.

(41) Radhakrishna, A. S., Parham, M. E.; Riggs, R. M.; Loudon, G. M. *J. Org. Chem.* **1979**, *44*, 1746.

***N*-(2-Bromo-α,α-dimethylbenzenemethyl)acetamide (19).** To a stirred solution of **13** (976 mg, 4.56 mmol) in CH_2Cl_2 (20 mL) was added first Et_3N (555 mg, 765 μL, 5.5 mmol) and then acetyl chloride (429 mg, 390 μL, 5.5 mmol) at 15 °C. The reaction mixture was stirred for 14 h at room temperature, diluted with CH_2Cl_2 (25 mL), washed first with water (25 mL), saturated aqueous $NaHCO_3$ solution (25 mL), and brine (25 mL). The organic phase was dried ($MgSO_4$) and concentrated to provide **19** as a white powder (1.04 g, 89%): ^{1}H NMR (200 MHz) δ 1.77 (s, 6H), 1.93 (s, 3H), 6.0 (br s, 1H), 7.04 (m, 1H), 7.27 (m, 1H), 7.51 (m, 2H); ^{13}C NMR (50 MHz) δ 23.4, 27.9, 55.8, 120.6, 127.5, 128.3, 135.4, 143.4, 168.9; MS (CI) *m*/*z* 258/256 (100, MH^+), 176 (100); HRMS calcd for $C_{11}H_{15}{}^{79}BrNO$ (MH^+) 256.0337, found *m*/*z* 256.0333; calcd for $C_{11}H_{15}{}^{81}BrNO$ 258.0317, found *m*/*z* 258.0307.

3,3-Dimethyl-1,2-benzisoselenazoline (15). General Procedure 1. To a solution of KSeCN (173 mg, 1.2 mmol) and **13** (214 mg, 1 mmol) in DMF (5 mL) was added at room temperature CuI (38 mg, 0.2 mmol for entries 2−3 in Table 1; 190 mg, 1 mmol, entries 4−5 in Table 1) in one portion, for entry 5 followed by Et_3N (303 mg, 420 μL, 3 mmol) 2 min later. The reaction mixture was stirred for 24 h at room temperature. To determine the conversion of **13**, 150 μL of the reaction mixture was diluted in 500 μL of acetone-d_6, and the signals of the dimethyl group in the ^{1}H NMR integrated: Amine **13**: 1.6−1.8 ppm, **15**: 1.5 ppm. To isolate **15**, the mixture was diluted with water (80 mL) and EtOAc (80 mL). After filtration through a pad of Celite, the organic phase was washed with water (5 × 50 mL) and brine (50 mL), dried ($MgSO_4$), and concentrated. Flash chromatography (cyclohexane/EtOAc = 9:1, R_f = 0.35) provided **15** in pale yellow crystals (32 mg, 15%, Table 1, entry 2; 85 mg, 40%, entry 4; 174 mg, 82%, entry 5): mp 38.5−39.5 °C; ^{1}H NMR (200 MHz) δ 1.50 (s, 6H), 4.10 (br s, 1H), 7.02−7.34 (m, 4H); ^{13}C NMR (50 MHz) δ 26.6, 70.8, 123.6, 124.4, 126.2, 128.1, 139.5, 149.6; ^{77}Se−NMR (47.7 MHz) δ 756.4. MS (EI) *m*/*z* 213 (30, M^+), 198 (100). Anal. Calcd for $C_9H_{11}NSe$: C, 50.95; H, 5.22; N, 6.60. Found C, 51.01; H, 5.17; N, 6.61.

General Procedure 2. To a solution of KSeCN (173 mg, 1.2 mmol) and **13** (214 mg, 1 mmol) in DMF (5 mL) was added at room temperature the metal salt in one portion, followed by Et_3N (303 mg, 420 μL, 3 mmol) 2 min later. After 24 and 40 h, respectively, a sample of 15 μL of the reaction mixture was diluted in 500 μL of acetone-d_6, and the signals of the dimethyl group in the ^{1}H NMR for **13** (1.6−1.8 ppm) and **15** (1.5 ppm) were integrated.

General Procedure 3. The reactions were performed as described in the General Procedure for Table 1, except for the variation of the solvent (5 mL) as given in each entry of Table 3. The product distribution was determined by ^{1}H NMR analysis on the crude reaction mixture obtained after the treatment as described before (see Table 1).

3,4-Dihydro-4,4-dimethyl-2*H*-1,2-benzoselenazine (21). General Procedure 4. To a stirred solution of **14** (228 mg, 1 mmol) and KSeCN (144−720 mg, 1−5 mmol, see Table 4) in DMF (entries 1−4, 5 mL), respectively, acetonitrile (entry 5), or THF (entry 6) was added CuI (190 mg, 1 mmol) in one portion, followed 2 min later by Et_3N (303 mg, 417 μL, 3 mmol). The reaction mixture was stirred at room temperature for 24 h and was then diluted with EtOAc (25 mL) and a solution of NaCN (147 mg, 3 mmol) in water (25 mL). After the mixture was stirred for 5 min, the organic phase was separated, and the aqueous phase was extracted again with EtOAc (25 mL). The combined organic phases were washed with water (5 × 40 mL) and brine (40 mL), dried (Na_2SO_4), and concentrated. To determine the conversion of **14** and the ratio of **21** to **22**, 20 mg of the crude product were dissolved in $CDCl_3$ and the signals of the dimethyl group in the ^{1}H NMR integrated at 1.26 ppm (**21**), 1.29 ppm (**22**), and 1.45 ppm (**14**).

Chromatography of the crude product on silica gel afforded **21** [R_f (hexane/EtOAc = 4:1) = 0.5] and 3,3-dimethylindolin **22** [R_f (hexane/EtOAc = 4:1) = 0.45] in colorless crystals.

21: 115 mg, 51% (Table 4, entry 1) and 154 mg, 68% (Table 4, entry 2), mp: 86 °C (hexane). ^{1}H NMR (200 MHz) δ 1.26 (s, 6H), 3.22 (br s, 2H), 3.45 (br s, 1H), 6.95−7.15 (m, 3H), 7.40 (m, 1H); ^{13}C NMR (50 MHz) δ 28.5, 33.0, 61.4, 125.5, 125.9, 126.8, 127.9, 129.9, 143.2; ^{77}Se−NMR (95 MHz) δ 693; MS (EI) *m*/*z* 227 (64, M^+), 183 (100). Anal. Calcd for $C_{10}H_{13}NSe$: C, 53.10; H, 5.79; N, 6.19. Found: C, 53.24; H, 5.77; N, 6.17.

3,3-Dimethylindolin (22): mp 33 °C (lit.[42] mp 32−33.5 °C); ^{1}H NMR (200 MHz) δ 1.34 (s, 6H), 3.35 (s, 2H), 3.70 (br s, 1H), 6.70 (m, 1H), 6.81 (m, 1H), 7.10 (m, 2H); ^{13}C NMR (50 MHz) δ 27.3, 41.5, 61.5, 109.6, 118.8, 122.0, 127.3, 138.5, 150.4; MS (EI) *m*/*z* 147 (20, M^+).

3,3-Dimethyl-1,2-benzisothiazoline (20). To a solution of KSCN (116 mg, 1.2 mmol) and **13** (214 mg, 1 mmol) in a mixture of THF (1 mL) and DMF (4 mL) was added at room temperature CuI (190 mg, 1 mmol) in one portion, followed by Et_3N (303 mg, 420 μL, 3 mmol) 2 min later. After being heated for 2 h at 80 °C, the reaction mixture was treated according to general procedure 1 to afford **20** as a slightly yellow oil (36 mg, 22%): ^{1}H NMR (200 MHz) δ 1.48 (s, 6H), 7.07 (m, 2H), 7.17 (m, 2H); ^{13}C NMR (50 MHz) δ 25.9, 69.6, 120.1, 122.2, 125.4, 127.9, 144.3, 146.4; MS (EI) *m*/*z* 165 (20, M^+), 150 (100), 109 (20); HRMS (EI) calcd for $C_9H_{11}NS$ (M^+) 165.0612, found *m*/*z* 165.0629.

3,4-Dihydro-4,4-dimethyl-2*H*-1,2-benzothiazine (23). Compound **23** was prepared starting from a solution of **14** (228 mg, 1 mmol) and KSCN (194 mg, 2 mmol) in THF/DMF (5 mL, 1:4). CuI (190 mg, 1 mmol) was added in one portion, followed 2 min later by Et_3N (303 mg, 417 μL, 3 mmol). Treatment of the reaction mixture, after heating for 2 h at 80 °C according to the procedure described for **21**, afforded **23** as colorless crystals (54 mg, 30%): mp 92 °C (hexane); ^{1}H NMR (200 MHz) δ 1.28 (s, 6H), 3.17 (br s, 2H), 6.86 (m, 1H), 7.04 (m, 2H), 7.36 (m, 1H); ^{13}C NMR (50 MHz) δ 29.1, 31.5, 59.9, 121.8, 125.2, 126.6, 127.8, 134.7, 140.5; MS (EI) *m*/*z* 179 (80, M^+), 149 (100), 134 (80); HRMS (EI) calcd for $C_{10}H_{13}NS$ (M^+) 179.0769, found *m*/*z* 179.0782.

2-(1′-Methyl-1′-ethylamino)phenylselenocyanate (16d). To a stirred solution of **15** (106 mg, 0.5 mmol) in acetonitrile (5 mL) was added NaCN (75 mg, 1.5 mmol). The homogeneous reaction mixture was stirred for 1 h at room temperature and was then diluted with water (20 mL) and EtOAc (20 mL). The organic phase was washed with water (5 × 20 mL), dried (Na_2SO_4), and concentrated to afford **16d** as a colorless oil (purity according to the ^{1}H and ^{13}C NMR ∼90%, the product contains ∼10% **15**[43]): ^{1}H NMR (200 MHz) δ 1.52 (s, 6H), 1.85 (br s, 2H), 7.10−7.28 (m, 3H), 7.91 (m, 1H), trace of **15** (about 10%) at 1.48 (s); ^{13}C NMR (50 MHz) δ 30.5, 54.4, 112.1, 125.9, 126.2, 127.6, 128.6, 131.4, 146.2, trace of **15** at 26 ppm. MS (EI) *m*/*z* 240 (22, M^+), 225 (50), 198 (100), 183 (50).

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(42) Abramovitch, R. A.; Brown, R. A. *Org. Prep. Proced.* **1969**, *1*, 39.

(43) Attempts to purify the crude product by chromatography over silica gel or alumina resulted in decomposition.