146. Phenylselenoacetaldehyde, a Useful Reagent for the Homologative Conversion of Halides to Phenylselenomethyl Ketones

by **Roger Baudat** and **Martin Petrzilka**

Département de Chimie Organique, Université de Genève, 30, quai Ernest Ansermet, CH-1211 Genève 4

Dedicated to Professor *Edgardo Giovannini* on his 70th anniversary

(27.IV.79)

Summary

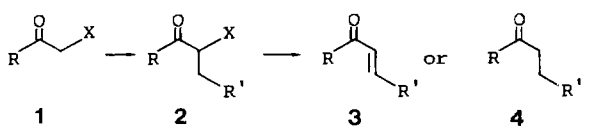
The conversion of primary, secondary and vinylic halides to the two C-atoms homologated phenylselenomethyl ketones **8** is described. The method involves addition of the readily available phenylselenoacetaldehyde **5** to the *Grignard* reagents **9** and oxidation of the resulting β-hydroxy-selenides **10** *(Scheme 3)*.

In contrast to simple methyl ketones **1** (X=H) phenylselenomethyl ketones **1** (X=SePh) may be alkylated regiospecifically. Oxidative elimination or reductive removal of the phenylseleno group of the resulting alkylated ketones **2** (X=SePh) then leads, respectively, to the α,β-unsaturated ketones **3** or the saturated ketones **4** [1] *(Scheme 1)*. Thus an easy access to this class of compounds is desirable, as reflected by three recent methods based on the regioselective addition of an electrophilic PhSeX species (X=Br [1] [2], X=$OSnBu_3$ [3]) to a terminal double bond.

Complementary to these functional group transformations we report a connective method, using phenylselenoacetaldehyde **5** as a two C-atoms homologation reagent. From our investigations on the electrophilic addition of benzeneselenenyl bromide to enol ethers [4], an effective method emerged for the preparation of this not readily accessible reagent **5**[1]) *(Scheme 2)*.

Addition of ethyl vinyl ether (**6**) to a solution of benzeneselenenyl bromide [4c] in absolute ethanol at 0° followed by hydrolysis of the crude diethyl acetal **7**

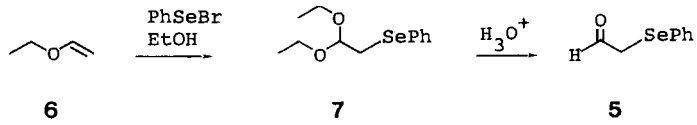
Scheme 1



[1]) Direct benzeneselenation of acetaldehyde according to *Sharpless* [5] furnished **5** in 35% yield after chromatographic purification.

0018-019X/79/5/1406-05$01.00/0

Scheme 2



Scheme 3

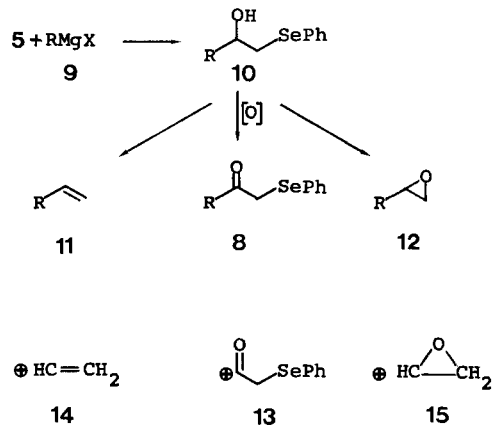
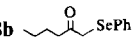
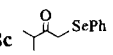
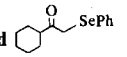
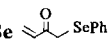
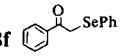
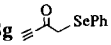


Table. *Yields of* **10** *and* **8**

Grignard reagent **9**	β-Hydroxy selenide **10**	Yield[a])	Phenylselenomethyl ketone **8**	Yield
9a CH_3MgI	**10a**	78%	**8a** 	61%[b])
9b 	**10b**	89%	**8b** 	74%[b])
9c 	**10c**	71%	**8c** 	60%[b])
9d 	**10d**	87%	**8d** 	74%[b])
9e 	**10e**	74%	**8e** 	63%[c])
9f 	**10f**	88%	**8f** 	71%[c])
9g 	**10g**	30%	**8g** 	0%[c])

[a]) Based on **5**. [b]) Method A: *N*-chlorosuccinimide-dimethylsulfide/NEt_3. [c]) Method B: DDQ.

(1N HCl/ether) afforded phenylselenoacetaldehyde (**5**) almost quantitatively. Its use for the preparation of phenylselenomethyl ketones **8** starting from organic halides is summarized in *Scheme 3*. Addition of **5** to a *Grignard* reagent **9** in ether at $-30°$ followed by normal work-up and chromatographic purification furnished the β-hydroxy selenides **10**, generally in high yields *(cf. Table)*. The *Grignard* reagents derived from primary, secondary and vinylic halides all reacted in the desired sense, whereas *t*-butylmagnesium chloride led only to decomposition products. The low yield obtained for the acetylenic β-hydroxy selenide **10g** might be due at least in part to its observed lower thermal stability. Since 2-hydroxy selenides **10** are convertible to terminal olefins **11** [6] and epoxides **12** [7], phenylselenoacetaldehyde (**5**) not only represents a synthon for **13** but also for **14** and **15** (see *Scheme 3*). Oxidation of **10** to **8** turned out to be more difficult than expected. For the saturated alcohols **10a–10d** various common oxidation reagents (*e.g.* pyridinium chlorochromate [8], pyridinium dichromate [9], dicyclohexylcarbodiimide-dimethylsulfoxide (DMSO) [10], trifluoroacetic anhydride-DMSO [11]) failed completely or gave the phenylselenomethyl ketones **8** in low yields[2]).

A major complication especially with the Cr(VI) reagents appeared to be the competitive oxidation of the phenylseleno group. However, much more satisfactory results were obtained using a slightly modified procedure (*cf.* exper. part, Method A) of the *Corey-Kim* oxidation [12]. In this way the phenylselenomethyl ketones **8a–8d** could be prepared in *ca.* 60–75% yield *(cf. Table)*.

On the other hand, the allylic alcohols **10e** and **10f**, which for known reasons (*cf.* [12] [13]) cannot be subjected to the above procedure, were oxidized to their ketone analogs **8e** and **8f** using 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing dioxane (*cf.* exper. part, Method B). No suitable conditions have yet been found for the related oxidation of the acetylenic β-hydroxy selenide **10g**.

We are currently exploring further the chemistry of some of these interesting reagents (*e.g.* **8e**) and their application to natural product synthesis.

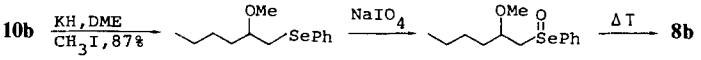
We thank Dr. *I. Grayson* for helpful comments and suggestions on the manuscript and Mr. *J.-P. Saulnier* and Mrs. *F. Klöti* for ^{1}H-NMR. and mass spectra measurements.

Experimental Part

General remarks. All reactions were carried out under argon. IR. spectra (CCl_4) are given in cm^{-1}. The chemical shift in ^{1}H-NMR.-spectra are given in ppm relative to tetramethylsilane as internal standard ($\delta = 0$). Multiplicities are expressed as singlet (*s*), doublet (*d*), triplet (*t*), quadruplet (*qa*), septuplet (*h*), multiplet (*m*). Spin-spin coupling constants (*J*) are given in *Hertz* (Hz). Aluminium oxide 90 *Merck* (activity II–III) and silica gel PF_{254} *Merck* (0.05–0.20 mm) were used for preparative chromatography. Abbreviations: br. broad, DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone.

Phenylselenoacetaldehyde diethylacetal (**7**). To a stirred solution of 4.72 g (20 mmol) of benzeneselenenyl bromide [4c] in 50 ml of abs. ethanol at 25° 2.1 ml (22 mmol) of neat ethyl vinyl ether (**6**) *(Fluka purum)* were added at once. The colour of the reaction mixture changed from dark orange to

[2]) Initial attempts to effect this transformation using the method of *Tsuji* [1] were not very successful. Accordingly, 1-phenylselenohexan-2-one (**8b**) was obtained in only 27% yield from the corresponding *O*-methylated β-hydroxy selenide.



light yellow. After stirring an additional 10 min, the reaction mixture was poured into sat. $NaHCO_3$-solution and extracted with ether (3×). The organic layers were washed with sat. $NaHCO_3$-solution (1×) and brine (1×), combined, dried (K_2CO_3) and concentrated *in vacuo* to afford 5.25 g (96%) of a slightly yellow[3]) liquid. For the following hydrolysis this material was used without further purification. An analytical sample of **7** was obtained by distillation, b.p. 80–82°/0.1 Torr. – IR.: 3050, 2970, 1582, 1480, 1380, 1350, 1110, 690. – ^{1}H-NMR.: 1.19 (*t*, *J* = 7, 6 H); 3.12 (*d*, *J* = 6, 2 H); 3.40–3.86 (*m*, 4 H); 4.75 (*t*, *J* = 6, 1 H); 7.18–7.42 (*m*, 3 H); 7.42–7.70 (*m*, 2 H). – MS.: 274 and 272 (M^+), 229, 183, 171, 157, 103 (100%), 91, 75 ($C_{12}H_{18}O_2Se$).

Phenylselenoacetaldehyde (**5**). A two-phase system consisting of a solution of 22.6 g (83 mmol) of phenylselenoacetaldehyde diethylacetal (**7**) in 500 ml of ether and 500 ml of 1N HCl was vigorously stirred for 24 h by means of a mechanical stirrer. After separation of the phases the aqueous layer was re-exctracted with ether (2×) and the organic layers were washed with water (2×) and brine (1×). Drying ($MgSO_4$) and removal of the solvent under reduced pressure afforded 16.1 g (98%) of a yellow[3]) liquid. An analytical sample of **5** was obtained by distillation, b.p. 57°/0.01 Torr. – IR.: 3065, 3055, 2825, 2720, 1710, 1580, 1480, 1440, 1400, 1150, 1025, 948, 692, 675 cm^{-1}. – ^{1}H-NMR.: 3.51 (*d*, *J* = 4, 2 H); 7.22–7.44 (*m*, 3 H); 7.44–7.68 (*m*, 2 H); 9.54 (*t*, *J* = 4, 1 H). – MS.: 200 (100%) and 198 (M^+), 171, 157, 117, 91, 77, 65, 51 (C_8H_8OSe).

1-Phenylselenohexan-2-ol (**10b**). To 20 ml (~20 mmol) of a ~1M solution of butylmagnesium bromide (**9b**) in dry ether at −30° a solution of 2.97 g (15 mmol) of phenylselenoacetaldehyde (**5**) in 10 ml of dry ether was added at such a rate that the temperature of the reaction mixture did not exceed −25°. After complete addition the mixture was allowed to reach RT. gradually and stirred for an additional 2 h. Then it was carefully quenched with aqueous saturated NH_4Cl-solution and extracted with ether (3×). The organic layers were washed with brine (1×), dried (K_2CO_3) and concentrated *in vacuo* to leave 3.45 g of crude product. Chromatography on silica gel with toluene/ethyl acetate 9:1 afforded 3.3 g (89%) of **10b** as a colourless oil. – IR.: 3560, 3450, 1580, 1480, 1439, 1380, 1072, 1022, 1000, 901. – ^{1}H-NMR.: 0.74–1.06 (tripletoid *m*, 3 H); 1.06–1.76 (*m*, 6 H); 2.69 (*s*, 1 H); 2.82–3.25 (AB-part of ABX-system, J_{AB} = 13, 2 H); 3.56–3.88 (X-part of ABX-system, 1 H); 7.12–7.70 (*m*, 2 H). – MS.: 258 and 256 (M^+), 201, 183, 172 (100%), 158, 157, 91, 83, 78, 76, 69, 55 ($C_{12}H_{18}OSe$).

1-Phenylselenopropan-2-ol (**10a**). – IR.: 3600, 3490, 3060, 1580, 1480, 1270, 1210, 1130, 1027, 938, 698, 675. – ^{1}H-NMR.: 1.28 (*d*, *J* = 6, 3 H); 2.54 (br. *s*, 1 H); 2.70–3.23 (*AB*-part of *ABX*-system, J_{AB} = 13, 2 H); 3.68–4.10 (*X*-part of *ABX*-system, 1 H); 7.20–7.70 (*m*, 5 H). – MS.: 216 (100%) and 214 (M^+), 172, 158, 98, 78, 77, 59, 51 ($C_9H_{12}OSe$).

3-Methyl-1-phenylselenobutan-2-ol (**10c**). – IR.: 3500, 3060, 1580, 1480, 1313, 1030, 992, 700, 678. – ^{1}H-NMR.: 0.93 and 0.96 (2 *d*, *J* = 7, 6 H); 1.58–1.97 (*m*, 1 H); 2.44 (br. *s*, 1 H); 2.30–3.30 (*AB*-part of *ABM*-system, J_{AB} = 12.5, 2 H); 3.32–4.60 (*M*-part of *ABM*-system, 1 H); 7.20–7.70 (*m*, 5 H). – MS.: 244 and 242 (M^+), 201, 183, 172 (100%), 157, 91, 78, 77, 69, 55, 51 ($C_{11}H_{16}OSe$).

1-Cyclohexyl-2-phenylselenoethanol (**10d**). – IR.: 3500, 3060, 2910, 2840, 1580, 1480, 1451, 1440, 1073, 1023, 980, 893, 695, 676. – ^{1}H-NMR.: 0.74–2.10 (br. *m*, 11 H); 2.48 (br. *s*, 1 H); 2.82–3.30 (*AB*-part of *ABM*-system, J_{AB} = 12.5, 2 H); 3.32–3.62 (*M*-part of *ABM*-system, 1 H); 7.10–7.70 (*m*, 5 H). – MS.: 284 and 282 (M^+), 183, 172, 157, 109, 95, 92, 91 (100%) ($C_{14}H_{20}OSe$).

1-Phenylselenobut-3-en-2-ol (**10e**). – IR.: 3580, 3480, 1635, 1578, 1480, 1440, 1025, 990, 931, 695, 675. – ^{1}H-NMR.: 2.63 (br. *s*, 1 H); 2.88–3.25 (*AB*-part of *ABX*-system, J_{AB} = 13, 2 H); 4.08–4.38 (*X*-part of *ABX*-system, 1 H); 5.16 (*d*×*t*, *J* = 10 and 1, 1 H); 5.29 (*d*×*t*, *J* = 16 and 1, 1 H); 5.91 (*d*×*d*×*d*, *J* = 16, 10 and 6, 1 H); 7.10–7.70 (*m*, 5 H). – MS.: 228 and 226 (M^+), 171, 158, 91 (100%), 78, 77, 71, 65, 57, 51 ($C_{10}H_{12}OSe$).

1-Phenyl-2-phenylselenoethanol (**10f**). – IR.: 3590, 3490, 3060, 1580, 1480, 1195, 1060, 1028, 975, 708, 699, 678. – ^{1}H-NMR.: 2.93 (br. *d*, 1 H); 3.00–3.38 (*AB*-part of *ABX*-system, J_{AB} = 12.5, 2 H); 4.62–4.86 (*X*-part of *ABX*-system, 1 H); 7.10–7.70 (*m*, 5 H). – MS.: 278 and 276 (M^+), 180, 172 (100%), 157, 120, 107, 91, 89, 87, 59 ($C_{14}H_{14}OSe$).

1-Phenylselenobut-3-yn-2-ol (**10g**). – IR.: 3590, 3450, 3300, 2125, 1580, 1480, 1440, 1055, 1030, 915, 699, 670, 645. – ^{1}H-NMR.: 2.47 (*d*, *J* = 2.5, 1 H); 2.98 (*d*, *J* = 6, 1 H); 3.22 (*d*, *J* = 6, 2 H); 4.50 (*qa*×*d*, *J* = 6

---

[3]) The yellow colour is due to a small amount of diphenyldiselenide present as the only impurity.

and 2.5, 1 H); 7.10–7.70 (*m*, 5 H). – MS.: 226 and 224 (M^+), 200, 171, 157, 91 (100%), 77, 51 ($C_{10}H_{10}OSe$).

Oxidation of **10a** *to phenylselenoacetone* (**8a**) *(Method A).* To a stirred solution of 100 mg (0.75 mmol) of *N*-chlorosuccinimide in 2.5 ml of dry CH_2Cl_2 was added at 0° 75 µl (1.05 mmol) of dimethyl sulfide. The resulting heterogeneous mixture was stirred for an additional 30 min before it was cooled to −20° and a solution of 107 mg (0.5 mmol) of **10a** in 0.5 ml of CH_2Cl_2 was added dropwise. After completed addition stirring was continued for 6 h at −20° and then 105 µl (0.75 mmol) of triethylamine were added dropwise. The cooling bath was removed and after 5 min the reaction mixture was poured into water and extracted with ether (3×). The organic layers were washed with brine (1×), dried ($MgSO_4$) and concentrated *in vacuo* to leave 95 mg of crude product. Chromatography on silica gel with hexane/ether 1:2 furnished 64 mg (60%) of **8a** as a colourless liquid. – IR.: 1710, 1580, 1480, 1365, 1230, 1030, 697, 678. – ^{1}H-NMR.: 2.26 (*s*, 3 H); 3.60 (*s*, 2 H); 7.20–7.70 (*m*, 5 H). – MS.: 214 and 212 (M^+), 171, 157, 117, 93, 91 (100%), 77 ($C_9H_{10}OSe$).

1-Phenylselenohexan-2-one (**8b**). – IR.: 1710, 1580, 1480, 1440, 1185, 1028, 698, 678. – ^{1}H-NMR.: 0.76–1.04 (tripletoid *m*, 3 H); 1.04–1.84 (br. *m*, 4 H); 2.50 (*t*, $J=7$, 2 H); 3.45 (*s*, 2 H); 7.10–7.60 (*m*, 5 H). – MS.: 256 and 254 (M^+), 213, 172, 157, 133, 91, 85 (100%), 77, 65, 57 ($C_{12}H_{16}OSe$).

3-Methyl-1-phenylselenobutan-2-one (**8c**). – IR.: 1710, 1580, 1480, 1390, 1200, 1158, 1035, 1028, 698, 678. – ^{1}H-NMR.: 2.11 (*d*, $J=7$, 6 H); 2.92 (*h*, $J=7$, 1 H); 3.70 (*s*, 2 H); 7.20–7.70 (*m*, 5 H). – MS.: 242 and 240 (M^+), 171, 157, 117, 91, 85, 77, 71 (100%), 51 ($C_{11}H_{14}OSe$).

Cyclohexyl(phenylselenomethyl)ketone (**8d**). – IR.: 1710, 1580, 1480, 1450, 1440, 1250, 1028, 1000, 696, 677. – ^{1}H-NMR.: 1.00–2.02 (br. *m*, 10 H); 1.40–1.70 (br. *m*, 1 H); 3.66 (*s*, 2 H); 7.20–7.70 (*m*, 5 H). – MS.: 282 and 280 (M^+), 234, 172, 157, 125, 111, 105, 91, 77, 55 (100%) ($C_{14}H_{18}OSe$).

Oxidation of **10f** *to phenylselenoacetophenone* (**8f**) *(Method B).* To a solution of 100 mg (0.36 mmol) of **10f** in 5 ml of dry dioxane at 25° was added a solution of 123 mg (0.54 mmol) of DDQ (*Fluka, purum*) in 5 ml of dry dioxane and the reaction mixture was brought to reflux for 6 h. Filtration through a short column of alumina (activity II–III), followed by chromatography on alumina (activity II–III) with hexane/ether 1:3 afforded 70 mg (71%) of **8f** as a colourless oil. – IR.: 1680, 1600, 1580, 1480, 1455, 1445, 1280, 1085, 1025, 1013, 710, 698, 678. – ^{1}H-NMR.: 4.17 (*s*, 2 H); 7.10–7.96 (*m*, 10 H). – MS.: 276 and 274 (M^+), 214, 171, 157, 120, 105 (100%), 91, 77, 59, 51 ($C_{14}H_{12}OSe$).

1-Phenylselenobut-3-en-2-one (**8e**). – IR.: 1680, 1615, 1580, 1480, 1440, 1400, 1268, 1200, 1070, 1025, 982, 696, 678. – ^{1}H-NMR.: 3.86 (*s*, 2 H); 5.82 (*d*×*d*, $J=10$ and 2, 1 H); 6.24 (*d*×*d*, $J=17$ and 2, 1 H); 6.58 (*d*×*d*, $J=17$ and 10, 1 H); 7.20–7.70 (*m*, 5 H). – MS.: 226 and 224 (M^+), 171, 157, 91 (100%), 84, 77, 69, 55 ($C_{10}H_{10}OSe$).

REFERENCES

[1] *T. Takahashi, H. Nagashima & J. Tsuji,* Tetrahedron Letters *1978,* 799.
[2] *S. Raucher,* Tetrahedron Letters *1978,* 2261.
[3] *I. Kuwajima & M. Shimizu,* Tetrahedron Letters *1978,* 1277.
[4] a) *M. Petrzilka,* Helv. *61,* 2286 (1978); b) *M. Petrzilka,* Helv. *61,* 3075 (1978); c) *R. Pitteloud & M. Petrzilka,* Helv. *62,* 1319 (1979).
[5] *K.B. Sharpless, R.F. Lauer & A.Y. Teranishi,* J. Amer. chem. Soc. *95,* 6137 (1973).
[6] *J. Rémion & A. Krief,* Tetrahedron Letters *1976,* 3743.
[7] a) *W. Dumont & A. Krief,* Angew. Chemie Int. Ed. *14,* 350 (1975); b) *D. Van Ende, W. Dumont & A. Krief,* Angew. Chemie Int. Ed. *14,* 700 (1973); c) *D. Van Ende & A. Krief,* Tetrahedron Letters *1976,* 457.
[8] *E.J. Corey & J.W. Suggs,* Tetrahedron Letters *1975,* 2647.
[9] *E.J. Corey & G. Schmidt,* Tetrahedron Letters *1979,* 399.
[10] *K.E. Pfitzner & J.G. Moffatt,* J. Amer. chem. Soc. *87,* 5661 (1965).
[11] *K. Omura, A.K. Sharma & D. Swern,* J. org. Chemistry *41,* 957 (1976).
[12] *E.J. Corey & C.U. Kim,* J. Amer. chem. Soc. *94,* 7586 (1972).
[13] *E.J. Corey, C.U. Kim & M. Takeda,* Tetrahedron Letters *1972,* 4339.