

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

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

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Summary

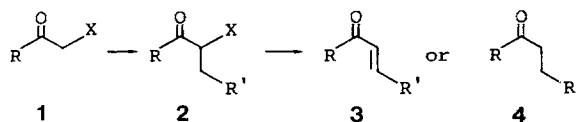
The conversion of primary, secondary and vinylic halides to the two C-atoms homologated phenylselenomethyl ketones **8** is described. The method involves addition of the readily available phenylselenoacetaldehyde **5** to the *Grignard* reagents **9** and oxidation of the resulting β -hydroxy-selenides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

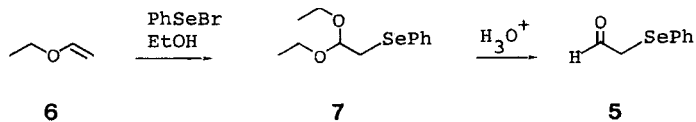
Addition of ethyl vinyl ether (**6**) to a solution of benzeneselenenyl bromide [4c] in absolute ethanol at 0° followed by hydrolysis of the crude diethyl acetal **7**

Scheme 1



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

Scheme 2



Scheme 3

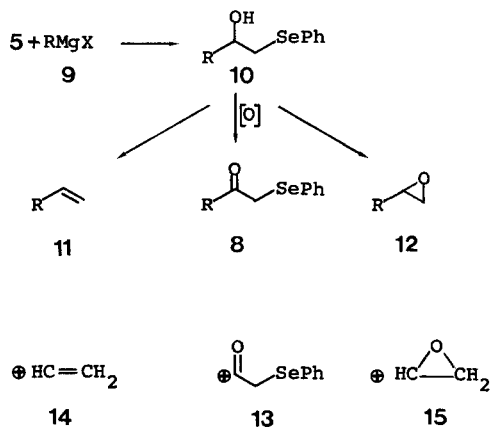


Table. Yields of 10 and 8

Grignard reagent 9	β -Hydroxy selenide 10	Yield ^{a)}	Phenylselenomethyl ketone 8	Yield
9a <chem>CH3MgI</chem>	10a	78%	8a <chem>CC(=O)CSePh</chem>	61% ^{b)}
9b <chem>CCCCMgBr</chem>	10b	89%	8b <chem>CCCC(=O)CSePh</chem>	74% ^{b)}
9c <chem>CC(C)MgBr</chem>	10c	71%	8c <chem>CC(C)C(=O)CSePh</chem>	60% ^{b)}
9d <chem>C1CCCCC1MgCl</chem>	10d	87%	8d <chem>C1CCCCC1C(=O)CSePh</chem>	74% ^{b)}
9e <chem>C#CCMgBr</chem>	10e	74%	8e <chem>C#CC(=O)CSePh</chem>	63% ^{c)}
9f <chem>c1ccccc1MgBr</chem>	10f	88%	8f <chem>c1ccccc1C(=O)CSePh</chem>	71% ^{c)}
9g <chem>C#CC#CCMgBr</chem>	10g	30%	8g <chem>C#CC#CC(=O)CSePh</chem>	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 yields²⁾.

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.

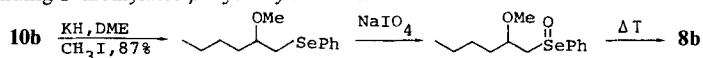
We thank Dr. I. Grayson for helpful comments and suggestions on the manuscript and Mr. J.-P. Saulnier and Mrs. F. Klöti for $^1\text{H-NMR}$. and mass spectra measurements.

Experimental Part

General remarks. All reactions were carried out under argon. IR. spectra (CCl_4) are given in cm^{-1} . The chemical shift in $^1\text{H-NMR}$ -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 PF₂₅₄ *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 benzene-selenenyl 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 ($3\times$). The organic layers were washed with sat. NaHCO_3 -solution ($1\times$) and brine ($1\times$), combined, dried (K_2CO_3) and concentrated *in vacuo* to afford 5.25 g (96%) of a slightly yellow³⁾ liquid. For the following hydrolysis this material was used without further purification. An analytical sample of **7** was obtained by distillation, b.p. $80\text{--}82^\circ/0.1$ Torr. - IR.: 3050, 2970, 1582, 1480, 1380, 1350, 1110, 690. - $^1\text{H-NMR.}$: 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 ($\text{C}_{12}\text{H}_{18}\text{O}_2\text{Se}$).

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-extracted with ether ($2\times$) and the organic layers were washed with water ($2\times$) and brine ($1\times$). Drying (MgSO_4) and removal of the solvent under reduced pressure afforded 16.1 g (98%) of a yellow³⁾ liquid. An analytical sample of **5** was obtained by distillation, b.p. $57^\circ/0.01$ Torr. - IR.: 3065, 3055, 2825, 2720, 1710, 1580, 1480, 1440, 1400, 1150, 1025, 948, 692, 675 cm^{-1} . - $^1\text{H-NMR.}$: 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 ($\text{C}_8\text{H}_8\text{OSe}$).

1-Phenylselenohexan-2-ol (10b). To 20 ml (~ 20 mmol) of a $\sim 1\text{M}$ 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 ($3\times$). The organic layers were washed with brine ($1\times$), 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. - $^1\text{H-NMR.}$: 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 ($\text{C}_{12}\text{H}_{18}\text{OSe}$).

1-Phenylselenopropan-2-ol (10a). - IR.: 3600, 3490, 3060, 1580, 1480, 1270, 1210, 1130, 1027, 938, 698, 675. - $^1\text{H-NMR.}$: 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 ($\text{C}_9\text{H}_{12}\text{OSe}$).

3-Methyl-1-phenylselenobutan-2-ol (10c). - IR.: 3500, 3060, 1580, 1480, 1313, 1030, 992, 700, 678. - $^1\text{H-NMR.}$: 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 ($\text{C}_{11}\text{H}_{16}\text{OSe}$).

1-Cyclohexyl-2-phenylselenoethanol (10d). - IR.: 3500, 3060, 2910, 2840, 1580, 1480, 1451, 1440, 1073, 1023, 980, 893, 695, 676. - $^1\text{H-NMR.}$: 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%) ($\text{C}_{14}\text{H}_{20}\text{OSe}$).

1-Phenylselenobut-3-en-2-ol (10e). - IR.: 3580, 3480, 1635, 1578, 1480, 1440, 1025, 990, 931, 695, 675. - $^1\text{H-NMR.}$: 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 ($d\times t$, $J=10$ and 1, 1 H); 5.29 ($d\times t$, $J=16$ and 1, 1 H); 5.91 ($d\times d\times d$, $J=16$, 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 ($\text{C}_{10}\text{H}_{12}\text{OSe}$).

1-Phenyl-2-phenylselenoethanol (10f). - IR.: 3590, 3490, 3060, 1580, 1480, 1195, 1060, 1028, 975, 708, 699, 678. - $^1\text{H-NMR.}$: 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 ($\text{C}_{14}\text{H}_{14}\text{OSe}$).

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

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 μ l (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 μ l (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 $\times$). The organic layers were washed with brine (1 $\times$), 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. – 1H -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. – 1H -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. – 1H -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. – 1H -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. – 1H -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. – 1H -NMR.: 3.86 (*s*, 2 H); 5.82 (*d* $\times$ *d*, *J* = 10 and 2, 1 H); 6.24 (*d* $\times$ *d*, *J* = 17 and 2, 1 H); 6.58 (*d* $\times$ *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 ($C_{10}H_{10}OSe$).

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