Syntheses of Alkali Selenolates from Diorganic Diselenides and Alkali Metal Hydrides: Scope and Limitations

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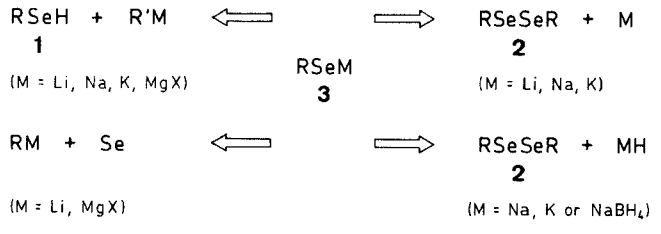
Sodium and potassium alkane[arene]selenolates have been efficiently prepared from the corresponding diselenides using sodium or potassium hydrides in dimethylformamide or tetrahydrofuran. The reaction cannot be extended for the production of their lithium analogues nor for sodium and potassium phenylmethaneselenolates.

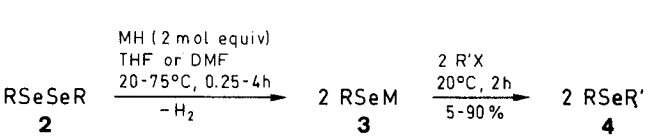
Selenolates **3** are valuable nucleophilic reagents which play a crucial role for the introduction of the seleno moiety in organic molecules.[1-5] They have been prepared i.a. from organometallics and elemental selenium,[6-8] on reaction of selenols **1** with bases,[9-20] and by reduction of (i) diselenides[10,13,21-32] **2** by metals[21-23] or metal hydrides[10,13,24-32] or (ii) selenocyanates[33,34] (Scheme 1). Although selenols **1** are acidic enough to be metalated with various bases including metal hydroxides, -alcoholates, -amides and -hydrides. The difficulties encountered for their synthesis[35] are very high oxidability and the volatility coupled with the particularly aggressive odor of the first members of the alkyl series which often restricted this approach. The reduction of diselenides **2** offers a much better solution since these compounds are usually readily prepared,[36-43] can be stored and handled without special precautions and are less volatile than the corresponding selenols. Furthermore, the reducing medium used, precludes the oxidation of the selenolates produced. Among the reducing agents commonly used for this purpose, sodium borohydride[25-31] has a place of choice and it offers definite advantage over other reagents due to the generality of the reaction, for example it allows the synthesis of the whole range of sodium aryl, alkyl[44] and benzyl selenides. However, the presence of boron compounds, produced along with the selenolate, changes in some cases dramatically its reactivity. Thus, whereas the benzene selenolate prepared from benzeneselenol and sodium hydride or from diphenyl diselenide and sodium borohydride exhibits almost the same reactivity towards alkyl halides[10] and epoxides,[30] the one prepared by the second method proved to be much less reactive especially towards esters and lactones.[45]



Scheme 1

In the course of a work directed towards a *medium scale* synthesis of selenomethionine,[32] we envisaged performing the reaction of methyl and benzyl sodium selenides with α-amino-γ-butyrolactone and found that the reaction is particularly sensitive to the presence of (i) water and (ii) boron compounds.[45] We therefore required an efficient method for the synthesis of sodium selenolates free from water and boron compounds. Hence we decided to prepare sodium methyl and benzyl selenides following the method described by Dowd[24] for the synthesis of sodium and potassium phenyl selenides (diphenyl diselenide, 2 molar equivalents of sodium hydride or potassium hydride, tetrahydrofuran, reflux, 1 hour, condition A refers to the use of tetrahydrofuran as the solvent).

We found that this reaction does not produce the desired amount of sodium methaneselenolate, the starting diselenide being recovered unchanged under these conditions (2 molar equivalents sodium hydride, tetrahydrofuran, reflux, 1 hour, condition A). We however noticed (Scheme 2) a great difference of reactivity, which was not perceivable from the original work, between sodium and potassium hydrides. The later being much more reactive allows the desired transformation (2 molar equivalents potassium hydride, tetrahydrofuran, reflux, 1 hour, 70 and 74% yield of methyl decyl and dibenzyl selenide after reaction of the selenolates with decyl bromide and benzyl chloride, respectively, 1 hour, 20°C, condition A).[46] In connection with this observation, we found that the reduction of diphenyl diselenide with potassium hydride is easily performed at room temperature (2 molar equivalents potassium hydride, tetrahydrofuran, 20°C, 1 hour, 88% yield of phenyl methyl selenide after reaction of the selenolate with methyl iodide, 20°C, 1 hour, condition A) whereas the one involving sodium hydride requires the use of conditions related to those originally described (2 molar equivalents sodium hydride, tetrahydrofuran, reflux, 2 hours, 87% yield of methyl phenyl selenide; compared with 20°C, 2 hours, < 5% yield).



Scheme 2

The above reported observations proved potassium hydride to be applicable to a wide range of diselenides. All the diselenides presented in Scheme 2 are usually readily cleaved by this reagent. However dialkyl diselenides require harder conditions (reflux, 1 to 3 hours) to produce a reasonably good yield of the potassium selenolates.[46] Interestingly the quite hindered di-*tert*-butyl diselenide is cleaved in 40% yield (unoptimized) under these conditions.[44]

In a parallel work, we surprisingly found that sodium hydride in tetrahydrofuran was not able to reduce dimethyl and dibenzyl diselenide but works properly for

Table 1. Reactions of Diselenides **2** with Bases and Subsequent Alkylation[a]

2–4	R	R'X	NaH/THF Yield (%) (°C, h)	NaH/DMF Yield (%) (°C, h)	KH/THF Yield (%) (°C, h)	KH/DMF Yield (%) (°C, h)
a	Ph	MeI	< 5 (20, 2); 87 (75, 1)	73 (20, 0.25)	88 (20, 1)	–
b	4-MeC_6H_4	MeI	87 (75, 1)	85 (20, 0.5)	–	–
c	4-ClC_6H_4	MeI	< 5 (20, 1); 90 (75, 1)	86 (20, 0.5)	–	–
d	Me	*n*-$C_{10}H_{21}Br$	< 5 (75, 2)	85 (20, 0.5)	70 (75, 1.25)	85 (20, 0.5)
e	Et	*n*-$C_{10}H_{21}Br$	25 (75, 3)	–	–	–
f	Pr	*n*-$C_{10}H_{21}Br$	60 (75, 2)	–	–	–
g	Bu	*n*-$C_{10}H_{21}Br$	74 (75, 0.75)	80 (75, 0.25)	80 (75, 1.25)	87 (20, 0.5)
h	*i*-Pr	*n*-$C_{10}H_{21}Br$	72 (75, 3)	70 (75, 1)	70 (75, 2)	–
i	*t*-Bu	*n*-$C_{10}H_{21}Br$	–	20 (75, 4)	41 (75, 3)	38 (75, 1)

[a] Yields refer to yield of compounds **4**.

Table 2. Spectroscopic Data of Compounds **4**

Compound	Molecular Formula	MS *m/z* (%)	^1H NMR (CCl_4/TMS) δ
4a	C_7H_8Se (172.0)	172 (100)	2.30 (s, 3H, CH_3Se), 7.00–7.50 (m, $5H_{arom}$)
4b	$C_8H_{10}Se$ (185.1)	186 (38)	2.30, 2.33 (2s, 6H, CH_3 and CH_3Se), 7.00, 7.30 (2d, $4H_{arom}$)
4c	C_7H_7ClSe (206.4)	206 (63), 208 (28)	2.33 (s, 3H, CH_3Se), 7.10–7.40 (m, $4H_{arom}$)
4d	$C_{11}H_{24}Se$ (235.3)	236 (30)	0.70–1.90 [m, 19H, $CH_3(CH_2)_8$], 1.90 (s, 3H, CH_3Se), 2.40 (t, 2H, CH_2Se)
4e	$C_{12}H_{26}Se$ (249.3)	250 (6.6)	0.66–1.80 (m, 22H, all H except CH_2SeCH_2), 2.30–2.70 (m, 4H, CH_2SeCH_2)
4f	$C_{13}H_{28}Se$ (263.3)	264 (6.9)	0.70–2.00 (m, 24H, all H except CH_2SeCH_2), 2.50 (t, 4H, CH_2SeCH_2)
4g	$C_{14}H_{30}Se$ (277.4)	278 (4.2)	0.66–2.00 (m, 26H, all H except CH_2SeCH_2), 2.55 (t, 4H, CH_2SeCH_2)
4h	$C_{13}H_{28}Se$ (263.3)	264 (7.2)	0.70–1.70 [m with d at 1.6, 25H, $(CH_3)_2C$, $CH_3(CH_2)_8$], 2.50 (t, 2H, CH_2–Se), 2.95 (quint, 1H, CH–Se)
4i	$C_{14}H_{30}Se$ (277.4)	278 (1)	0.85 (t, 3H, CH_3CH_2), 1.15–1.70 [m with s at 1.57, 25H $(CH_3)_3C$, $(CH_2)_8CH_2Se$], 2.5 (t, 2H, CH_2Se)

higher homologues. We unexpectedly observed that this reaction becomes easier with lengthening of the alkyl chain (Scheme 2). At present time we cannot explain these facts and we are currently working on this problem.

We have been able to efficiently reduce dimethyl diselenide using sodium hydride by performing the reaction in dimethylformamide instead of tetrahydrofuran (condition B refers to the use of dimethylformamide as solvent). In this solvent, the reaction takes place very rapidly at room temperature (2 molar equivalents, sodium hydride, dimethylformamide, 20 °C, 0.5 hour, 85% yield of decyl methyl selenide after reaction of the selenolate with decyl bromide, 20 °C, 1 hour, condition B). Furthermore, the sodium methyl selenide generated in this way is able to promote efficiently the ring opening of lactones. This method allows the synthesis of a wide range of alkyl and phenyl selenides in good yields (Scheme 2).

In comparison, lithium hydride proved to be a very poor reducing agent since it is able to cleave only the diaryl diselenides although in poor yields, even under ideal and harder conditions in dimethylformamide (diphenyl diselenide, 75 °C, 3 hours, condition B; 24% yield of methyl phenyl selenide after reaction of the lithium selenolate and methyl iodide).

It is worth to note from the above results, condition B proved to be always much more efficient than condition A by promoting the reduction of dialkyl and diaryl diselenides by sodium and potassium hydride as well. However under these conditions, the reaction takes a completely different course when applied to dibenzyl diselenide and this will be subject of a forthcoming paper.

^1H NMR spectra were measured on Jeol JNM 60Si or FX 90Q spectrometers using CCl_4 as solvent and TMS as internal standard. Mass spectra were recorded on HP 5995 A GC/MS spectrometer at 78 eV. The microanalysis were performed in the Microanalysis Laboratory of the Paris VI University. Layer chromatography: analytical TLC was made on aluminum sheets pre-coated with silica gel, 60 PF 254, 0.25 mm (Merck 5554). Compounds were visualized by UV illumination and by heating to 150 °C after spraying phosphomolybdic acid in EtOH. PLC was performed on silica gel plates prepared in our laboratory.[38] Anhydrous THF and DMF were obtained by distillation on sodium benzophenone ketyl and CaH_2, respectively (18 Torr). NaH (80% dispersion in mineral oil) and KH (30% dispersion in mineral oil) were purchased from Janssen Chimica and Merck, respectively. Both hydrides were used without removal of the oil.

Diphenyldiselenide, bis(4-methylphenyl)diselenide, bis(4-chlorophenyl) diselenide and di-*tert*-butyl diselenide were synthesized by oxidation of the corresponding selenols with sodium perborate.[41] Dimethyl diselenide was prepared in one-pot from elemental Se by the classical procedure.[38,39] Diethyl, dipropyl, dibutyl and diisopropyl diselenides were synthesized from the corresponding alkyl bromide and lithium diselenide according to an original method.[42] All these diselenides are known for long time[36] and even the ^{77}Se NMR data of most of them have been reported.[43]

Reduction of Diselenides 2 Followed by Alkylation; General Procedure:

To a suspension of MH (2.10^{-3} m in oil) in a solvent (1 mL) under Ar, was added at 20 °C a solution of **2** (1.10^{-3} m) in the same solvent (1 mL). The reaction was allowed to proceed (time and temperature are listed in Table 1). Then, a solution of the alkyl halide (2.10^{-3} m) in the same solvent (2 mL) was introduced at 20 °C. After 2 h, H_2O (3 mL) was added. The resulting mixture was extracted with Et_2O (2 × 20 mL). The organic extracts were combined and washed with H_2O (2 × 5 mL), dried ($MgSO_4$), evaporation of the solvent furnished a crude oil which was purified by PLC (silica gel; pentane) to afford the pure selenide. The nature of the solvent was disclosed for each specific case in Table 1.

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(44) During the course of this work, we have been able to reduce, although in very poor yield, di-*tert*-butyl diselenide, under usual conditions, with $NaBH_4$ in EtOH (3.5 mol. equiv $NaBH_4$, EtOH, 20°C, 1 h, 19% yield).
(45) This observation has already been described on less functionalized lactones.[13,22,24,29,32,42]
(46) Although it is possible to prepare potassium methylselenolate in THF, this reagent is unable to promote the ring opening of γ-butyrolactones in this solvent.