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LETTERS

Synthesis of diselenides and selenides from elemental selenium

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Abstract—Sodium hydride is able to reduce elemental selenium to sodium diselenide (Na_2Se_2), but not to sodium selenide (Na_2Se). Dialkyl diselenides and even dialkyl selenides, including unsymmetrical dialkyl selenides, can be nevertheless synthesized using the proper Se/NaH ratio (1/1 or 1/2). © 2002 Elsevier Science Ltd. All rights reserved.

Over the last 25 years, organoselenium chemistry has been the subject of constant scientific interest and has been used intensively.[1] Organoselenium compounds are no longer systematically classified as toxic and some of them can be bought not only from the chemical companies, but also in several supermarkets as a food supplement.

The synthesis of organoselenium compounds always implies at some stage the reaction with elemental selenium **1**. For example elemental selenium reacts: (i) directly with organometallics (1 equiv.) to produce organic selenolates and (ii) with several reducing agents to produce selenides (Se^{--}) or diselenides ($^{-}SeSe^{-}$). These, after reaction with electrophilic organic species such as akylhalides or -pseudohalides, lead to diorganyl selenides **3** or diorganyl diselenides **4**, respectively.[1]

Alkaline metals in liquid ammonia[2] or in the presence of an electron carrier in THF,[3] zinc in the presence of sodium hydroxide,[4] samarium diiodide,[5] metal borohydrides[6] and hydrazine[7] in basic media are among the reagents to allow, when used in stoichiometric amounts, the efficient synthesis of metal diselenides. The same reagents, with the exclusion of hydrazine, are also able to generate dimetal selenides if used in at least twice the amount.

We have now found that sodium hydride **2** is an efficient reagent for the synthesis of sodium diselenide in dimethylformamide (DMF), which is also one of the most appropriate solvents for alkylation reactions. The reaction is best achieved at 70°C for 2 h, using 1.1 mol equiv. of sodium hydride per mole of gray selenium. Alkylation has been carried out at room temperature using 1 mol equiv. of alkylating agent. Under these conditions dialkyl diselenides **4** are produced besides only a trace amount of dialkyl selenides **3** and dialkyl triselenides **5** from which they can be easily freed by distillation or by chromatography on silica gel (Table 1).

Although the reduction of elemental selenium can be carried out at lower temperature, it is less selective and produces higher amounts of **3** and **5** at the expense of **4**.

The synthesis of diorganic diselenides has been also performed in other solvents such as dimethyl sulfoxide (DMSO), *N*-methylpyrrolidinone (NMP), dimethoxy-

Table 1. Synthesis of dialkyl diselenides according to Scheme 1

Entry	RX	**3**/**4**/**5** ratio[a]	**4** (Yield%)
1	MeI	–/97/3[b]	**4a** (60)
2	Me_2SO_4	–/92/8	**4a** (72)
3	*n*-BuBr	3/89/8[c]	**4b** (70)
4	*n*-DecBr	0/91/9	**4c** (80)
5	*i*-PrBr	0/100/0	**4d** (88)
6	*s*-BuBr	0/88/12	**4e** (70)
7	$PhCH_2Br$	6/90/4	**4f** (75)

[a] Most of the products have been already described.[2–7]
[b] Dimethyl selenide is too volatile to be detected by GC under the conditions used.
[c] ^{1}NMR ($CHCl_3$, δ ppm): **3**/**4**/**5** M/D/D.

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$$\underset{\mathbf{1}}{\mathrm{Se}} + 1.1\ \underset{\mathbf{2}}{\mathrm{NaH}} \xrightarrow[\text{(ii) RX, 20°C, 1h}]{\text{(i) DMF, 70°C, 2h}} \underset{\mathbf{3}}{\mathrm{RSeR}} + \underset{\mathbf{4}}{\mathrm{RSeSeR}} + \underset{\mathbf{5}}{\mathrm{RSeSeSeR}}$$

Scheme 1.

ethane (DME) or tetrahydrofurane (THF), but none of them proved as effective as DMF. For example, excellent selectivity has been observed in DMSO at 70°C, but the overall yields were modest, whereas poor selectivities and yields have been found in NMP.

We have also carried out the reduction of elemental selenium reaction with a different Se/NaH ratio (1/2 instead of 1/1.1) expecting the synthesis of sodium selenide at first and dialkyl selenides **3** after alkylation.

When the reaction is performed with 2 mol equiv. of NaH (DMF, 70°C, 2 h) and butyl bromide (2 mol equiv., 20°C, 4 h, conditions A) dibutyl selenide **3b** is produced but mixed with substantial amounts of dibutyl diselenide **4b** (Scheme 2, entry 1).

This could suggest that sodium selenide is the effective intermediate. We were nevertheless surprised to get:

(i) a much poorer **3**/**4** ratio when longer straight chain or branched chain alkyl bromides are used instead (Table 2, entries 2–4)

(ii) significant amounts of the unexpected dibenzyl selenoacetal of benzaldehyde **7f** besides dibenzyl selenide **3f** on reaction with benzyl bromide (14/86 ratio; 43% isolated yield of dibenzyl selenide) (Scheme 3)[8]

(iii) substantial amounts of the dissymmetric *n*-butyl *i*-propyl selenide **8a** with very high selectivity on sequential addition, on the reduced selenium species, of mol equiv. of two different alkyl halides [(i) *n*-butyl bromide (0°C, 0.2 h; 20°C, 2 h) then (ii) *i*-propyl bromide (20°C, 4 h) (Scheme 4, entry 1)].

$$\underset{\mathbf{1}}{\mathrm{Se}} + 2.1\ \underset{\mathbf{2}}{\mathrm{NaH}} \xrightarrow[\text{(ii) Conditions A or B}]{\text{(i) DMF, 70°C, 4 h}} \underset{\mathbf{3}}{\mathrm{RSeR}} + \underset{\mathbf{4}}{\mathrm{RSeSeR}}$$

Scheme 2.

Such selectivity is unusual since it has been mentioned in the literature on several occasions that the one-pot sequential reaction of metal selenides with two different alkyl halides or -pseudo halides leads to an intractable mixture of all the possible selenides.[6] This suggests that (i) metal selenides and the related metal alkylselenolates possess a very close nucleophilicity and (ii) sodium selenide is not produced on reaction of gray selenium with 2 mol equiv. of NaH in DMF (Scheme 5).

We therefore proposed an alternative pathway (Scheme 6 instead of Scheme 5), to explain the formation of dialkyl selenides **3** on sequential addition on elemental selenium of sodium hydride (2 equiv.) and alkyl bromide (2 equiv.). It involves:

(i) the formation of sodium diselenide, leaving unreacted half of the amount of the sodium hydride introduced (Scheme 6, step a)

(ii) dialkylation of sodium diselenide to produce dialkyl diselenide, leaving an unreacted amount (half) of the introduced alkyl halide (Scheme 6, step b)

(iii) cleavage of the dialkyl diselenide by the unreacted sodium hydride to generate sodium alkylselenolate (Scheme 6, step c)[8]

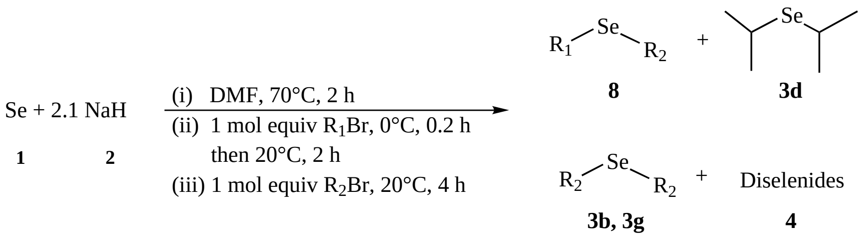
Table 2. Synthesis of dialkyl selenides according to Scheme 2

Entry	RX	Conditions A		Conditions B	
		3/**4** ratio	**3** (%)[a]	**3**/**4** ratio	**3** (%)[a]
1	*n*-BuBr	87/13	**3b** (64)	89/11	**3b** (67)
2	*n*-HexBr	62/38	**3g** (38)	89/11	**3g** (67)
3	*n*-DecBr	67/33	**3c** (33)	94/6	**3c** (59)
4	*i*-PrBr	50/50	**3d** (–)	93/7	**3d** (50)

[a] Yields in analytically pure compounds.

$$\underset{\mathbf{1}}{\mathrm{Se}} + 2.1\ \underset{\mathbf{2}}{\mathrm{NaH}} \xrightarrow[\text{(ii) 2 mol equiv PhCH}_2\text{Br, 20°C, 1h}]{\text{(i) DMF, 70°C, 1 h}} \underset{\mathbf{3f}\ 86\ \%}{\mathrm{PhCH_2SeCH_2Ph}} + \underset{\mathbf{7f}\ 14\ \%}{\mathrm{PhCH(SeCH_2Ph)_2}}$$

Scheme 3.



Scheme 4.

$$\begin{array}{lrcl}
\text{(a)} & 2\,\text{Se} + 4\,\text{NaH} & \longrightarrow & [2\,\text{NaSeNa}] + 2\,\text{H}_2 \\
\text{(b)} & [2\,\text{NaSeNa}] & \xrightarrow{4\,\text{RBr}} & 2\,\text{RSeR} + 4\,\text{NaBr} \\
\hline
\text{(e)} & 2\,\text{Se} + 4\,\text{NaH} + 4\,\text{RBr} & \longrightarrow & 2\,\text{RSeR} + 4\,\text{NaBr} + 2\,\text{H}_2
\end{array}$$

Scheme 5.

$$\begin{array}{lrcl}
\text{(a)} & 2\,\text{Se} + 4\,\text{NaH} & \longrightarrow & [\text{NaSeSeNa} + \mathit{2\,NaH}] + \text{H}_2 \\
\text{(b)} & [\text{NaSeSeNa} + \mathit{2\,NaH}] & \xrightarrow{4\,\text{RBr}} & [\text{RSeSeR} + 2\,\text{NaBr} + \mathit{2\,NaH} + \mathit{2\,RBr}] \\
\text{(c)} & [\text{RSeSeR} + \mathit{2\,NaH} + \mathit{2\,RBr}] & \longrightarrow & [2\,\text{RSeNa} + \mathit{2\,RBr}] + \text{H}_2 \\
\text{(d)} & [2\,\text{RSeNa} + \mathit{2\,RBr}] & \longrightarrow & 2\,\text{RSeR} + 2\,\text{NaBr} \\
\hline
\text{(e)} & 2\,\text{Se} + 4\,\text{NaH} + 4\,\text{RBr} & \longrightarrow & 2\,\text{RSeR} + 4\,\text{NaBr} + 2\,\text{H}_2
\end{array}$$

Scheme 6.

(iv) alkylation of sodium alkylselenolates by the unreacted alkyl halide (Scheme 6, step d).

In order to determine the real pathways (Scheme 5 or Scheme 6 for example), we decided to monitor, by volumetric titration, the amount of dihydrogen released after addition of each reagent involved in the synthesis of dialkyl selenides. For example, the amount of dihydrogen expelled prior to addition of any alkyl bromide should be twice the amount, if Scheme 5 is operative, of that expected if the reaction instead follows the pathway disclosed in Scheme 6.

Since some of the steps of this synthesis could be identical to those implied in the related synthesis of dialkyl diselenides (which only differs in that the Se/Na ratio is 1/1 instead of 1/2, Scheme 7), we have, for comparison purposes, monitored the amount of dihydrogen produced during the synthesis of dialkyl diselenides.

We observed that the reaction between equivalent amounts of selenium and sodium hydride (5 mmol each) produces 58 ml of dihydrogen (61 ml [2.5 mmol] of dihydrogen expected, Scheme 7, step a). This fully agrees with the formation of sodium diselenide. Addition of 2 equiv. of *n*-butyl bromide provides dibutyl diselenide (80% yield, Scheme 7, R = Bu) and as expected no more dihydrogen is formed (Scheme 7, step b).

Performing the reaction with twice the amount of sodium hydride (10 mmol, Se/NaH ratio: 1/2), produces 69 ml of dihydrogen. This supports the formation of sodium diselenide (61 ml [2.5 mmol] of dihydrogen expected, Scheme 6, step a) and rules out the formation of sodium selenide which would have instead produced 122 ml of dihydrogen (5 mmol, Scheme 5, step a).

$$\begin{array}{llcl}
\text{(a)} & 2\,\text{Se} + 2\,\text{NaH} & \longrightarrow & [\text{NaSeSeNa}] + \text{H}_2 \\
\text{(b)} & [\text{NaSeSeNa} + 2\,\text{RBr}] & \longrightarrow & \text{RSeSeR} + 2\,\text{NaBr}
\end{array}$$

Scheme 7.

Addition, at that stage, of 2 mol equiv. (10 mmol) of *n*-butyl bromide leads to the production of (i) 50 ml of dihydrogen, (61 ml [2.5 mmol] expected, Scheme 6, step c) and (ii) dibutyl selenide. These results unambiguously support the sequence of reactions disclosed in Scheme 6.

Another support for this hypothesis arises from the formation of dibutyl diselenide (94% yield) instead of dibutyl selenide, when water is added prior to the addition of *n*-butyl bromide (2 mol equiv.). This is due to the destruction of the unreacted sodium hydride which produces dihydrogen concomitantly (77 ml, expected 61 ml, Scheme 8). Related results have been obtained when propionic acid or aqueous hydrochloric acid replaced water (dibutyldiselenide formed: 92% yield, dihydrogen produced: 62 ml, expected 61 ml, in each case).

We have used this information to propose a modified and more appropriate experimental procedure to generate dialkyl selenides, which involves sequential addition of each of the 2 equiv. of the alkyl halide [(i) elemental selenium, 2 mol equiv. of NaH, DMF, 70°C, 2 h, (ii) 1 mol equiv. R_1Br, 0°C, 0.2 h, (iii) 20°C, 2 h, (iv) 1 mol equiv. R_2Br 20°C, 6 h, conditions B, Scheme 2, Table 2]. These conditions significantly improve the yields in symmetrical selenides (Table 2, compare conditions B to conditions A).

- It takes into account the observation that the two alkyl groups present on the dialkyl selenide are not delivered just one after the other as would have been the case if sodium selenide was involved (compare Scheme 6, steps b, d and Scheme 5).
- It avoids the reaction between sodium hydride and the second mol equiv. of the alkylating agent which

$$\text{(a)}\quad 2\ \text{Se} + 4\ \text{NaH} \xrightarrow[\text{4 h}]{\text{DMF, 70°C}} [\text{NaSeSeNa} + \textit{2 NaH}] + \text{H}_2$$

$$\text{(b)}\quad [\text{NaSeSeNa} + \textit{2 NaH}] \xrightarrow[\text{20°C, 1h}]{\text{excess H}_2\text{O}} [\text{NaSeSeNa} + 2\ \text{NaOH}] + 2\ \text{H}_2$$

$$\text{(c)}\quad [\text{NaSeSeNa} + \textit{2 NaOH}] \xrightarrow{\text{4 BuBr}} \underset{94\ \%}{\text{BuSeSeBu}} + 2\ \text{NaBr} + \textit{2 NaOH} + \textit{2 BuBr}$$

Scheme 8.

Table 3. Synthesis of dissymmetric dialkyl selenides according to Scheme 4

Entry	R_1Br	R_2Br	**8**/**3d**/**3b**,**g**/**4** ratio	**8** (Yield%)
1	*n*-BuBr	*i*-PrBr	90/10	68
1	*n*-HexBr	*i*-PrBr	90/7/3	61
2	*i*-PrBr	*n*-HexBr	16/31/39/13	–

could compete with the cleavage of the intermediate dialkyl diselenide.

- It allows the quite selective synthesis of dialkyl selenides bearing two different alkyl groups, but only when the first alkylating agent is primary (Table 3, compare entry 2 to entry 3).

We are trying to improve the conditions for the one-pot synthesis of unsymmetrical dialkylselenides and we will apply the results described in this letter to the synthesis of functionalized diselenides and selenides.

References

1. (a) Rheinboldt, H. In *Schwefel-, Selen-, Tellur-Verbindungen Methoden der Organische Chemie* (*Houben Weyl*); Müller, E., Ed.; Georg Thieme: Stuttgart, 1967; Vol. 9; (b) *Organic Selenium Compounds: Their Chemistry and Biology*; Klayman, D. L.; Günther, W. H. H., Eds.; John Wiley and Sons: Chichester, 1973; (c) Paulmier, C. In *Selenium Reagents and Intermediates in Organic Synthesis*; Baldwin, J. E., Ed.; Pergamon: Oxford, 1986; Vol. 5; (d) *The Chemistry of Organic Selenium and Tellurium Compounds*; Patai, S.; Rappoport, Z., Eds.; John Wiley and Sons: Chichester, 1987; Vol. 2; (e) Krief, A. In *Comprehensive Organometallic Chemistry II*; Abel, E. W.; Stone, F. G. A.; Wilkinson, G.; McKillop, A., Eds.; Pergamon: Oxford, 1995; Vol. 11, p. 516.
2. Brandsma, L.; Wijers, H. E. *Rec. Trav. Chim.* **1963**, *82*, 68–74.
3. (a) Thompson, P. *Boujouk* **1988**, *53*, 2109–2112; (b) Syper, L.; Mlochowski, J. *Tetrahedron* **1988**, *44*, 6119–6130.
4. Ping, L.; Xunjun, Z. *Synth. Commun.* **1993**, *23*, 1721–1725.
5. (a) Klayman, D. L.; Griffin, T. S. *J. Am. Chem. Soc.* **1973**, *95*, 197–199; (b) Gladysz, J. A.; Hornby, J. L.; Garbe, J. E. *J. Org. Chem.* **1978**, 1204–1208; (c) Bergman, J.; Engman, L. *Synthesis* **1980**, 569–570; (d) Yarada, K.; Fujita, T.; Yanada, R. *Synlett* **1998**, 971–972.
6. (a) Zang, Y.; Jia, X.; Zouh, X. *Synth. Commun.* **1994**, *24*, 1247–1252; (b) Jia, X.; Zang, Y.; Zouh, X. *Synth. Commun.* **1993**, *23*, 1403–1408.
7. (a) Syper, L.; Mlochowski, J. *Synthesis* **1984**, 439–442; (b) Eggert, H.; Nielsen, O.; Henriksen, L. *J. Am. Chem. Soc.* **1986**, *108*, 1725–1730; (c) Li, J. Q.; Bao, W. L.; Lue, P.; Zhou, X.-J. *Synth. Commun.* **1991**, *21*, 799–806.
8. (a) Krief, A.; Trabelsi, M.; Dumont, W. *Synthesis* **1992**, 933–935; (b) Krief, A.; Trabelsi, M.; Dumont, W. *Synlett* **1992**, *8*, 638–640.