Conditions-Driven Selective Synthesis of Selenides and Selenols from Elemental Selenium

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In memoriam Dr Anne Giese, née Ghosez, for her contribution to the development of Organic Chemistry through Synlett.

Abstract: Sodium borohydride in DMF is able to reduce elemental selenium in the presence of ethanol. Alkylation of the species resulting from the reaction of 2:1 molar equivalents of $NaBH_4$/Se allows the selective synthesis, under very mild conditions, of symmetrical dialkyl selenides. Addition of formic acid, prior to that of the electrophile, permits the synthesis of the corresponding selenols.

Key words: elemental selenium, sodium borohydride, alkylation, alkyl halides, benzyl halides

Selenides **1** are valuable synthetic intermediates[1] which have been often prepared by alkylation of metal selenides (MSeM)[1] or organic selenolates (RSeM).[1]

Those, as well as metal hydroselenides (HSeM),[1] are available by reduction of elemental selenium either by metals,[2] or by metal hydrides,[3] metal hydroxymethanesulfinates[4] and organometallics.[5]

Sodium borohydride[3a] was the first hydride used for that purpose. It possesses the advantage to be commercially available and is easy to handle but the reaction is limited. It has been carried out on benzyl chloride, one of the most reactive electrophile, in water whose use is inadequate for organic reactions.

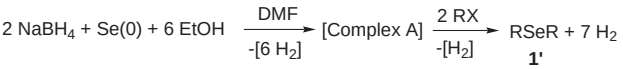
Ammonium borohydride[3c] and borohydride[3d] exchange resin have been proposed as alternative reagents. The later avoids the inconveniencies reported above and allows the synthesis of a few primary dialkyl selenides as well as a primary and a secondary benzyl selenide, but the method carries its proper limitations.[3d]

Synthesis of Symmetrical Dialkyl Selenides 1′

We now report that symmetrical dialkyl selenides **1′** can be efficiently produced in DMF from elemental selenium, two molar equivalents of sodium borohydride and two equivalents of alkyl halides at the condition that 6 equivalents of ethanol are present in the medium prior the alkylation step (**Complex A**).[3f]

This complex is prepared by adding ethanol to a selenium–sodium borohydride solid mixture maintained at 20 °C. The alkylation is then performed at room temperature on the colourless solution of that complex in DMF. Performing the reaction in that order avoids the formation of by products resulting from the decomposition of DMF.

The reaction proceeds extremely well at room temperature providing primary and secondary dialkyl and dibenzyl selenides in very high yield (Scheme 1, Table 1). Interestingly, dialkyl diselenides **2**, which are often concomitantly formed in the synthesis of dialkyl selenides **1′**, have not been found using our procedure (Scheme 1).



Scheme 1 Synthesis of symmetrical selenides **1′**

Table 1 Reaction Conditions of the Synthesis of Dialkyl Selenides **1′**

Entry	RX	**1′**:**2**	Yield (%) of **1′**
a	*n*-Bu-Br	100:0	93
b	*n*-Dec-Br	100:0	100
c	$PhCH_2$-Br	100:0	97
d	$PhCH_2$-Cl	100:0	95
e	*sec*-Octyl-Br	100:0	92
f	*sec*-Bu-Br	100:0	92
g	*iso*-Pr-I	100:0	91
h	PhCH(Me)-Br	100:0	98

The amount of ethanol used is not crucial for the reaction to proceed at the condition that it is higher than 6 equivalents and not so high that it plays the role of the solvent.[3f] Other alcohols such as *i*-propanol and *t*-butanol can be used in place of ethanol. However, they do not offer specific advantages. Methanol should not be used since it reacts too rapidly with sodium borohydride.

We have carefully monitored the evolution of hydrogen generated in this process and found that 6 molar equivalents escape from the medium (experimentally 97% of this amount) just before the alkyl halide is added and another

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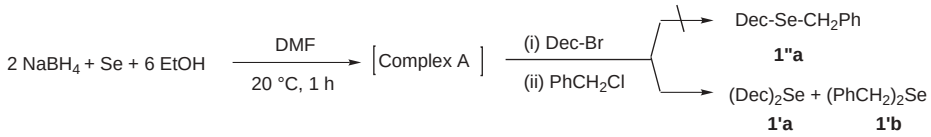
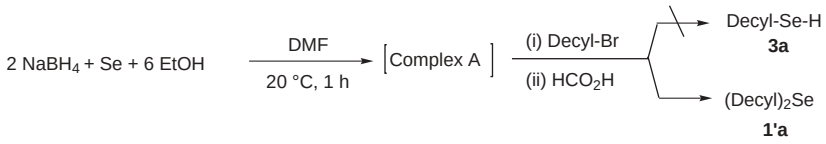


Scheme 2



Scheme 3

one (experimentally 1.2 molar equivalents of this amount) on addition of the alkyl halide.

We also found that almost no hydrogen is evolved if ethanol is missing in this mixture (experimentally 0.4 equiv H_2 produced).[3f] This suggests that addition of selenium to the mixture of sodium borohydride and ethanol enhances the reactivity of these two species.

Sequential addition of two different alkyl halides (R_1X and R_2X, 1 equiv each) to the **Complex A**, disclosed above, does not allow the selective synthesis of the mixed selenide[3b] **1″** but leads instead to one to one mixture of the two possible symmetrical selenides **1′** (Scheme 2, **1′a**: 50% **1′b**: 50%).

Furthermore, sequential addition of decyl bromide and formic acid does not produce decylselenol **3a** but leads instead to didecyl selenide **1′a** (49% relative Se; 97% relative to decyl bromide, Scheme 3).

Synthesis of Selenols 3

We have been able to synthesise selectively decylselenol **3a** by simply interchanging the order of addition of decyl bromide and formic acid (Scheme 4, Table 2, entry a).

The reaction proved to be general and allows quite selectively the synthesis of a large array of primary and secondary alkyl- and benzyl-selenols at the condition that 2.5 equivalents of formic acid are used with alkyl halides and 4 equivalents with benzyl halides (Table 2, entries d, f, g; compare entry d to c and f to e).

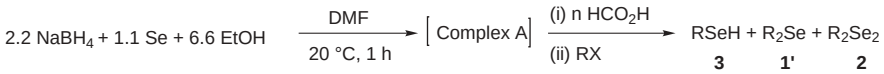
Table 2 Reaction Conditions of the Synthesis of Alkyl Selenols **3**

Entry	n	RX	**3**:**1**:**2**	Yield (%) of **3**
a	2.5	*n*-Dec-Br	97:0/3	91
b	2.5	*n*-Hex-Br	96:0:4	76
c	2.5	$PhCH_2$-Br	73:27:0	48
d	4	$PhCH_2$-Br	93:0.7:0	69
e	2.5	$PhCH_2$-Cl	88:0:12	63
f	4	$PhCH_2$-Cl	98:0:2	76
g	4	PhCH(Me)-Br	100:0:0	78
h	2.5	*sec*-Octyl-Br	78:0:8	76

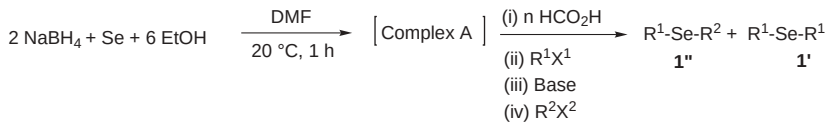
Synthesis of Unsymmetrical Dialkyl Selenides 1″

We have used this finding to develop a multistage procedure to synthesise unsymmetrical dialkyl selenides **1″** in a single pot (Scheme 5, Table 3). This novel method takes advantage of (i) the efficient synthesis of selenols **3** reported above and (ii) the fact that selenols **3** do not react with alkyl halides in the absence of a base.[6]

We have thus introduced in the reaction medium enough base to neutralise formic acid and to transform the alkyl selenols **3** to alkyl selenolates prior the addition of the alkylating agent [(i) 2 equiv $NaBH_4$, DMF (ii) 1 equiv Se (iii) EtOH, 20 °C, 0.5 h (iv) 4 equiv HCO_2H (v) 1 equiv R^1X^1, 20 °C, 4 h (vi) 5 equiv NaOH or 4 equiv NaH



Scheme 4 Synthesis of alkyl selenols **3**



Scheme 5 Synthesis of unsymmetrical dialkyl selenides **1″**

Table 3 Reaction Conditions of the Synthesis of Unsymmetrical Dialkyl Selenides

Entry	R^1X^1	R^2X^2	Base	**1″**:**1′**	Yield (%) of **1″**
a	*n*-Bu-Br	*sec*-Octyl-Br	5 equiv NaOH	100:0	69
b	*sec*-Octyl-Br	*n*-Bu-Br	5 equiv NaOH	80:20	60
c	*n*-Dec-Br	*n*-Bu-Br	4 equiv NaH	90:10	78
d	*n*-Dec-Br	*iso*-Pr-I	4 equiv NaH	84:12	67
e	*sec*-Octyl-I	*iso*-Pr-I	4 equiv NaH	95:05	66
f	$PhCH_2$-Cl	*iso*-Pr-I	4 equiv NaH	85:15	60

(vii) R^2X^2, 20 °C, 2–4 h]. Under these conditions unsymmetrical dialkyl selenides **1″** bearing primary- or secondary alkyl or benzyl groups have been produced in fair yield (60–78%). Small amount of the symmetrical dialkyl selenides **1′** has been separated after distillation.

Conclusion

The real nature of the species involved in the formation of symmetrical dialkyl selenides **1′**, selenols **3** and unsymmetrical substituted dialkyl selenides **1″** is not well defined and this is attested by (i) the presence in the medium of boron derivatives, probably complexed triethylborate (ii) the gas volumetric measurement reported at the beginning of this work which parallels the synthesis of dialkyl selenides and which does not correspond to a well define stoichiometry.

The presence of ethanol is essential[3f] and probably allows the substitution of hydrides on boron by ethoxide groups. Ethanol can also play the role of the solvent but the reactions are slower and the yields of dialkyl selenides **1″** poorer.

Anyhow, (i) the former reagent plays the role of a selenide dianion (Se^{2-}), which is the precursor of symmetrical dialkyl selenides **1′** on alkylation (ii) addition of formic acid to the medium allows the formation of a reagent which plays the role of hydroselenide anion (HSe^-)[7] the precursor of alkyl selenols **3** on alkylation (iii) treatment of the later in situ with a base is expected to produce a reagent which plays the role of alkyl selenolate anions (RSe^-) the precursor of unsymmetrical selenides **1″** on alkylation.

Depending on the conditions used symmetrical selenides **1′**, unsymmetical selenides **1″** and selenols **3** can be selectively synthesised in high yield from readily available and easily handled sodium borohydride, elemental selenium and alkyl halides. Those reactions provide a large variety of these organoselenium compounds at the exclusion of those derived from tertiary alkyl- or tertiary benzyl halides. We are currently working to apply our finding to the synthesis of dialkyl diselenides **2**.

Typical Procedures

Synthesis of Complex A. A solid mixture of sodium borohydride (0.38 g, 10 mmol) and elemental selenium (0.40 g, 5 mmol) is stirred in a two naked flask under argon and maintained at 20 °C using a water bath. Dropwise addition of anhydrous EtOH (1.40 g, 30 mmol) to this mixture favours the rapid evolvement of hydrogen and produces a white-grey solid. Addition of anhydrous DMF (10 mL) produces a red-brown solution, which slowly leads to a colourless one (**Complex A**).

Synthesis of Symmetrical Dialkyl- and Dibenzyl-selenides 1′ from Complex A.

Alkyl- or benzyl halide (10 mmol) is added dropwise to the solution of **Complex A** reported above. The resulting milky medium is stirred before hydrolysis and extraction with Et_2O as reported in Scheme 1.

Synthesis of Alkyl and Benzyl Selenols 3 from Complex A.

Addition of formic acid (0.575 g, 12.5 mmol for alkyl halides or 0.92 g, 20 mmol for benzyl halides) to the solution of **Complex A**, reported above, initiates the formation of hydrogen and the production of a white precipitate. The electrophile (5 mmol) is then added and the resulting suspension is stirred for 2–5 h prior to hydrolysis and extraction of the selenol with Et_2O (Scheme 4).

Synthesis of Unsymmetrical Dialkyl- and Dibenzyl-selenides 1″ from Complex A.

Addition of formic acid (0.575 g, 12.5 mmol) to the stirred solution of **Complex A** reported above, initiates the formation of hydrogen and the production of a white precipitate. The first equivalent of alkyl halide (5 mmol) is then added dropwise and the resulting white mixture is stirred at r.t. for at least 4 h prior the addition of the base (20–25 mmol). This leads to the formation of large amounts of a precipitate. The second electrophile (5 mmol) is then subsequently introduced and the mixture stirred for 2–4 h more prior to hydrolysis and extraction with Et_2O (Scheme 5).

References

(1) (a) Rheinboldt, H. *Schwefel-, Selen-, Tellur-Verbindungen, In Methoden der Organische Chemie (Houben Weyl)*, Vol. 9; Müller, E., Ed.; Georg Thieme: Stuttgart, **1967**. (b) *Organic Selenium Compounds: Their Chemistry and Biology*; Klayman, D. L.; Gunther, W. H. H., Eds.; John Wiley and Sons: Chichester, **1973**. (c) *Selenium in Natural Products Synthesis*; Nicolaou, K. C.; Petasis, N. A., Eds.; Cis Inc.: Philadelphia, **1984**. (d) Paulmier, C. In *Selenium Reagents and Intermediates in Organic Synthesis*, Vol. 5; Baldwin, J. E., Ed.; Pergamon: Oxford, **1986**. (e) *The Chemistry of Organic Selenium and Tellurium Compounds*, Vol. 2; Patai, S.; Rappoport, Z., Eds.; John Wiley and Sons:

Chichester, **1987**. (f) Krief, A. In *Comprehensive Organometallic Chemistry II*, Vol. 11; Abel, E. W.; Stone, F. G. A.; Wilkinson, G.; McKillop, A., Eds.; Pergamon: Oxford, **1995**, 516. (g) *Organoselenium Chemistry: A Practical Approach*; Back, T. G., Ed.; University Press: Oxford, **1999**. (h) *Organoselenium Chemistry: Modern Developments in Organic Synthesis*; Wirth, T., Ed.; Springer-Verlag: Berlin, **2000**.

(2) (a) Brandsma, L.; Wijers, H. E. *Recl. Trav. Chim. Pays-Bas* **1963**, *82*, 68. (b) Shlyk, Y. N.; Bogolyubov, G. M.; Petrov, A. A. *Zh. Obshch. Khim.* **1968**, *38*, 1199. (c) Thompson, D.; Boudjouk, P. *J. Org. Chem.* **1988**, *53*, 2109. (d) Ping, L.; Xunjun, Z. *Synth. Commun.* **1993**, *23*, 1721.

(3) (a) Klayman, D. L.; Griffin, T. S. *J. Am. Chem. Soc.* **1973**, *95*, 197. (b) Gladysz, J. A.; Hornby, J. L.; Garbe, J. E. *J. Org. Chem.* **1978**, *43*, 1204. (c) Bergman, J.; Engman, L. *Synthesis* **1980**, 569. (d) Yanada, K.; Fujita, T.; Yanada, R. *Synlett* **1998**, 971. (e) Ishihara, H.; Koketsu, M.; Fukuta, Y.; Nada, F. *J. Am. Chem. Soc.* **2001**, *123*, 8408. (f) The reaction between sodium borohydride (2 equiv) and selenium, carried out in pure DMF also leads to a complex that can be successfully alkylated to **1′** but contaminated by a minor impurity difficult to separate from **1′**. However, these conditions do not allow the synthesis of the selenol **3** if formic acid is added prior to the alkylating agent (compare to Scheme 4).

(4) Bird, M. L.; Challenger, F. *J. Chem. Soc.* **1942**, 570.

(5) Krief, A.; Van Wemmel, T.; Redon, M.; Dumont, W.; Delmotte, C. *Angew. Chem. Int Ed.* **1999**, *38*, 2245; and references cited therein.

(6) In the course of this work we have found that whereas decyl selenol **3a** does not react with decyl bromide or methyl iodide in DMF, it can be alkylated if the reaction is carried out in the presence of sodium formate (1 equiv). The reaction is quite slow (20 °C, 20 h) and provides competitively some diselenides **2** resulting from the oxidative coupling of the selenolates.

(7) (a) Wood, R. H. *J. Am. Chem. Soc.* **1958**, *80*, 1559. (b) Goldbach, A.; Saboungi, M.-L.; Johnson, J. A.; Cook, A. R.; Meisel, D. *J. Phys. Chem. A* **2000**, *104*, 4011.