



General synthesis of alkyl phenyl selenides from organic halides mediated by zinc in aqueous medium

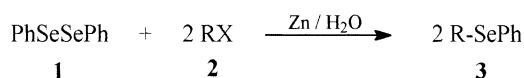
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Abstract—Organic halides of different structural types react with diphenyl diselenide and zinc dust in aqueous medium to give alkyl phenyl selenides. Benzylic and allylic bromides, α -bromoesters, acids and ketones and some primary alkyl iodides produce high yields even under acidic conditions. Less reactive halides need basic medium. The reaction proceeds equally well in the presence of various unprotected functional groups. Control experiments support a S_H2 mechanism via alkyl radicals. © 2001 Elsevier Science Ltd. All rights reserved.

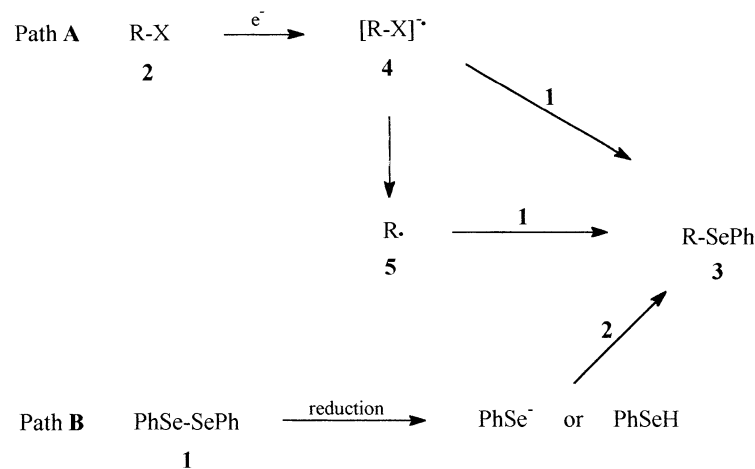
Alkyl phenyl selenides are versatile intermediates in organic synthesis especially for the mild introduction of C=C double bonds.¹ Several general and high yielding preparative methods have been developed using reagents such as phenyl selenol or diphenyl diselenide **1** in nucleophilic displacement reactions. In the first case, a phenyl selenolate anion reacts with organic halides or sulfonates, in the second the same species is the leaving group displaced by enolates. Both procedures require basic conditions and the second one has to be performed under strictly anhydrous conditions limiting thus the scope to base resistant substrates. Alternatively, there are several recent reports of Chinese scientists dealing with the reaction of diselenides with bromoketones,² bromoesters,³ allyl,⁴ propargyl⁴ and benzyl⁵ bromides promoted by In, Sn, Cd and Zn in neutral aqueous media. Although satisfactory yields of the corresponding mixed selenides have been obtained in several examples, these special procedures could not be extended to other classes of halides; furthermore, the use of In and Cd in preparative scale is not advisable for economical and environmental reasons. We present here a simple, general and high yielding preparation of alkyl phenyl selenides using commercial zinc dust in aqueous medium.



We started our experiments with α -bromoesters, allylic and benzylic halides which can react through resonance

stabilized intermediates and are highly efficient in aqueous Barbier-type reactions.^{6–8} First attempts under similar conditions using monobasic or dibasic phosphate solutions without any cosolvent led exclusively to reduction of the halide leaving diphenyl diselenide (**1**) unchanged. Addition of acetonitrile or dioxane to dissolve **1** circumvented this problem; complete consumption of the reagents was observed in a few minutes and high yields of phenylselenyl-substituted compounds **3** were obtained in both acidic and basic medium. A great number of structurally different halides was reacted under these two standard conditions (Table 1). In concentrated dibasic potassium phosphate solution (pH ~ 12), alkyl halides gave good to excellent yields (entries 1–4); acidic, neutral or strongly basic conditions lowered the yield, except for secondary iodides which gave best results in KOH solution (entries 5 and 6). With tertiary alkyl halides (R = *t*-butyl and adamantyl, entries 7–9) only modest yields were obtained under these conditions, but the use of large excess of *t*-butyl iodide improved the yield significantly even in this case. More reactive halides such as ethyl iodide, allyl and benzyl bromide and several α -haloesters, acids, nitriles and ketones gave high yields even in monobasic sodium phosphate solution (pH ~ 4). In contrast to Barbier-type additions to carbonyl compounds⁶ and Wurtz-type couplings,⁹ substituted allylic and propargylic halides produced exclusively the unrearranged isomers (entries 12–17, 28, 29). In some cases chlorides gave better yields than bromides, probably because the latter were too reactive and reduction became predominant under basic conditions (entries 12 versus 13, 15 versus 16, 18 versus 19, 20 versus 21 and 28 versus 29). A similar reasoning may explain the advantage to use granulated

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Scheme 1.

Table 1. Synthesis of alkyl phenyl selenides from diphenyl diselenide (**1**) and organic halides **2** in aqueous medium promoted by Zn^a

Entry	Halide 2	Yield 3 (%)	
		NaH ₂ PO ₄ solution	K ₂ HPO ₄ solution
1	Et-I	85	100
2	ⁿ Bu-I	28	82
3	ⁿ Bu-Br	0	78
4	^t BuCH ₂ -I	0	95
5	^t Pr-I	5	72 ^c
6	<i>cyclo</i> -C ₆ H ₁₁ -I	0	84 ^c
7	^t Bu-I	0	16 (61) ^d
8	^t Bu-Br	0	3
9	Adamantyl-I	0	10
10	CH ₂ =CHCH ₂ -Br	100	89
11	CH ₂ =CHCH ₂ -Cl	24	45
12	CH ₃ CH=CHCH ₂ -Br	60	66
13	CH ₃ CH=CHCH ₂ -Cl	24	78
14	(CH ₃) ₂ C=CHCH ₂ -Br	20 (63) ^b	69
15	HCCCH ₂ -Br	21	42
16	HCCCH ₂ -Cl	10	76
17	CH ₃ CCCH ₂ -Br	34 (41) ^b	73
18	PhCH ₂ -Br	100	63
19	PhCH ₂ -Cl	45	100
20	(CH ₃) ₃ CCOCH ₂ -Br	0 (11) ^b	27 (51) ^b
21	(CH ₃) ₃ CCOCH ₂ -Cl	62	76
22	EtOCOCH ₂ -Br	77	84
23	EtOCOCH ₂ -Cl	70	90
24	EtOCOCH(CH ₃)-Br	41 (80) ^b	64
25	EtOCOC(CH ₃) ₂ -Br	0	51
26	NCCH ₂ -Br	33	53 (60) ^b
27	NCCH ₂ -Cl	72	29
28	PhCH=CHCH ₂ -Br	0 (33) ^b	0 (25) ^b
29	PhCH=CHCH ₂ -Cl	54	100
30	ClCH ₂ -I	50	77
31 ^c	HOOCCH ₂ -Br	50 (83) ^b	0
32 ^c	HOOCCH ₂ -Cl	95	0
33 ^c	HOOCCH(CH ₃)-Br	67	0
34	EtOCOCH ₂ CH ₂ -Br	62	98
35	HOCH ₂ CH ₂ -Br	35	93
36	NC(CH ₂) ₄ Br	85	89

^a Typical procedure: To a solution of 1.0 g of the indicated salt in 1.0 mL of water **1** (0.125 mmol) and **2** (0.5 mmol) dissolved in 0.5 mL of CH₃CN were added. Under vigorous stirring Zn dust was added over a period of 10 min. After stirring for 1 h, the mixture was hydrolyzed and extracted with 1.0 mL of CCl₄ containing 0.2 mmol of anisole as internal quantitative reference. The yield was determined in the crude extract by ¹H NMR or GC-MS.

^b Granulated Zn was used.

^c An aqueous solution of 0.5 g of KOH was used.

^d 0.025 mmol of **1** and 0.5 mmol of ^tBuI were used.

^e Extraction with CHCl₃.

zinc instead of dust in various examples (entries 14, 17, 20, 24, 26, 28 and 31).

An important feature of this aqueous procedure is the tolerance of several additional functional groups. Halogenated carboxylic acids, esters, nitriles and alcohols gave preparative yields, some of them even in acidic medium (entries 31–36).

The reaction described here can be explained by two different reaction mechanisms (Scheme 1). By path A, the halide **2** reacts with the metal in a single electron transfer (SET) producing a radical species **4** or **5** which will attack **1** in a S_H2 reaction. Indeed, free radicals **5**, generated photolytically, are known to give this reaction in the presence of **1**.¹⁰ In path B, diselenide **1** is reduced first to selenol or its anion which can displace the halide in a S_N2 reaction. Experimental support in this question was obtained, when **1** was reduced first by Zn or sodium borohydride and then the halide was added. Although this two-step reaction in basic medium produced yields comparable to the one-step procedure with primary and secondary halides, in a neutral buffer the yields were much lower and only trace amounts of **3** were obtained in acidic medium. *t*-Butyl iodide gave no coupling at all. Furthermore, most halides used here reacted easily with Zn alone, whereas **1** is reduced very slowly under the reaction conditions. Based on these results, we must conclude that path A should predominate in basic medium and be almost exclusive under acidic conditions. A more detailed study of the radical mechanism, especially the nature of the radical intermediate **4** or **5**, will be the object of further investigations.

Acknowledgements

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