

Communications

A Mild and Efficient Method for Preparing Alkyl Phenyl Selenides from Alkyl Diphenyl Phosphinites

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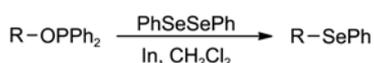
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Alkyl phenyl selenides have recently attracted considerable interest since they can be used as precursors for various organic transformations.¹ Additionally, selenides have played an important role in biochemical processes serving as therapeutic compounds ranging from antiviral and anti-cancer agents to naturally occurring food supplements.² Although numerous methods for preparing alkyl phenyl selenides have been reported,³ these methods sometimes suffer from difficulties in handling the selenide reagent used as the selenium source, strongly basic or acidic reaction conditions, and low yields of tertiary alkyl phenyl selenides.⁴

Recently, we reported a mild procedure for the preparation of alkyl phenyl selenides from alkyl halides using PhSeSePh in the presence of In.⁵ This protocol has a number of advantages including a simple experimental procedure, neutral pH and mild reaction conditions, and high yields of the desired products even in the case of tertiary alkyl phenyl selenides. In an attempt to extend the scope of our methodology, we decided to explore the preparation of alkyl phenyl selenides under our conditions using a new type of precursor, alkyl diphenyl phosphinites (Scheme 1).

The latter can be simply prepared from the corresponding alcohols by reacting with ClPPh₂, Et₃N and DMAP.⁶ Many reports have demonstrated the use of these phosphinites as key intermediates for oxidation-reduction condensations to prepare a variety of organic functional groups such as isocyanates, diorganyl sulfides, esters, ethers, and others.⁷ However, there are no reported methodologies for preparation of alkyl phenyl selenides *via* phosphinites. Thus, the present work focused on the development of an efficient and mild procedure for the synthesis of alkyl phenyl selenides from alkyl diphenyl phosphinites with PhSeSePh in the presence of In. Reaction parameters, such as reaction solvents and mole ratios of reagents, were varied to establish optimal reaction conditions.



Scheme 1

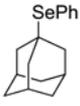
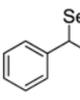
Reaction of 1-adamantyl diphenyl phosphinite with PhSeSePh in the presence of In under various reaction conditions was investigated (Table 1). At room temperature, the reaction proceeded for 24 h to give 1-adamantyl phenyl selenide in 47% yield, whereas a similar yield could be attained in a shorter reaction time at reflux (entries 1 and 2) with half of the starting material still remained. When the amount of 1-adamantyl diphenyl phosphinite and In were 1:1.5, respectively, the desired product were furnished in 53% yield at room temperature after 24 h and in 83% yield after refluxing for 2 h (entries 3 and 4). In the absence of In, the reaction did not proceed, which revealed the necessity of In for the reaction (entry 5).

The scope and limitations of this methodology were investigated by treating various alkyl diphenyl phosphinites (1 equiv) with PhSeSePh (1 equiv) in the presence of In (1.5 equiv) in CH₂Cl₂ at reflux to afford a wide range of alkyl phenyl selenides (Table 2). Under these conditions, primary and tertiary alkyl phenyl selenides could be attained in high yields (entries 1-5). Similarly, preparations of benzyl and allyl phenyl selenides were also achieved (entries 6-8). Allyl diphenyl phosphinite is more reactive than the substituted allyl diphenyl phosphinite (entries 7 and 8). Acyclic secondary alkyl diphenyl phosphinites underwent clean reactions to provide the corresponding alkyl phenyl selenides in high

Table 1. Synthesis of 1-adamantyl phenyl selenide from 1-adamantyl diphenyl phosphinite

Entry	ROPPh ₂ (equiv)	PhSeSePh (equiv)	In (equiv)	Temp	Time (h)	Isolated yield (%)
1	1	0.5	3	rt	24	47
2	1	0.5	3	reflux	2	45
3	1	1	1.5	rt	24	53
4	1	1	1.5	reflux	2	83
5	1	1	0	reflux	2	0

Table 2. Synthesis of alkyl phenyl selenides from alkyl diphenyl phosphinites

Entry	RSePh	Time (h)	Isolated yield (%)
1	$t\text{BuSePh}$	2	71
2	 SePh	2	83
3	$\text{CH}_3(\text{CH}_2)_6\text{SePh}$	2	96
4	$\text{CH}_3(\text{CH}_2)_{15}\text{SePh}$	2	89
5	$\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_6\text{SePh}$	2	80
6	 SePh	3	89
7	 SePh	2	78
8	 SePh	2	69
9	$\text{CH}_3(\text{CH}_2)_5\text{CHCH}_3$ SePh	4	98
10	$\text{CH}_3(\text{CH}_2)_9\text{CHCH}_3$ SePh	3	86
11	 SePh	4	0
12	 SePh	2	28 ^a
13	 SePh	24	0 (23) ^b

^aAnalyzed by GC. ^bThe reaction was carried out in the presence of I_2 (0.5 equiv) for 4 h.

yields. However, longer reaction times were required compared to reactions using primary and tertiary phosphinites (entries 9 and 10). On the other hand, diphenyl methyl phenyl phosphinite was unreactive even when the reaction time was extended to 4 h (entry 11). In the case of cyclic secondary alkyl diphenyl phosphinites, the reaction did not proceed smoothly. Cyclohexyl phenyl selenide was obtained in 28% yield (entry 12), and the reaction with cyclododecyl diphenyl phosphinite did not proceed at all (entry 13). There have been many reports of reactions using metals that were promoted by the addition of I_2 .⁸ The conversion of cyclododecyl diphenyl phosphinite was tried in the presence of 0.5 equiv of I_2 and afforded the corresponding phenylselenide albeit in moderate yield (entry 13). We speculate that adding I_2 under these reaction conditions enhanced the rate of reaction.

A series of experiments was performed to gain some insight into the reaction pathway. Reactions of 1-adamantyl diphenyl phosphinite with only PhSeSePh or with only In failed to proceed, whereas the reaction of PhSeSePh and In yielded a yellow solution. These results clearly revealed that the reaction commenced with the interaction of PhSeSePh and In to afford $\text{In}(\text{SePh})_3$.⁹ It has been reported that selenides could be synthesized through a radical pathway initiated by In.^{3a,5} To probe whether the reaction proceeds by a free radical process, the reaction of 1-hexadecanyl diphenyl

yl phosphinite was performed under standard conditions in the presence of galvinoxyl free radical.¹⁰ The corresponding phenyl selenide was obtained in 87% yield, which was not different from the same reaction in the absence of radical scavenger. Finally, the reaction of an optically active substrate, (*R*)-(-)-2-octanol ($[\alpha]_{\text{D}}^{25} -9.4$ (*c* 1.0, CH_2Cl_2)) could be successfully transformed into the chiral (*S*)-(+)-2-octyl phenylselenide ($[\alpha]_{\text{D}}^{26} +15.2$ (*c* 1.0, CH_2Cl_2)) with complete conversion. It is therefore clear that under optimized conditions, this reaction proceeded *via* an $\text{S}_{\text{N}}2$ mechanism. In the case of tertiary alkyl phenyl selenides, the mechanistic pathway possibly proceeds by an $\text{S}_{\text{N}}1$ process driven by formation of a strong P=O bond in diphenylphosphine oxide to generate a tertiary carbocation intermediate.

In summary, we developed an efficient method for preparing alkyl phenyl selenides by the In-mediated reaction of alkyl diphenyl phosphinites with PhSeSePh. Significant advantages of the method are short reaction times, neutral and mild reaction conditions, and high isolated yields of the products even in the case of tertiary alkyl phenyl selenides.

The general procedure is as follows: a mixture of alkyl diphenyl phosphinite (0.5 mmol), PhSeSePh (156.1 mg, 0.5 mmol) and In powder (86.1 mg, 0.75 mmol) in dried CH_2Cl_2 (20 mL) was heated at reflux for 2 h under argon. The reaction mixture was quenched with 1 M HCl. The organic layer was washed with brine, dried over anhydrous MgSO_4 , and purified by column chromatography on silica gel eluting with hexane to give the corresponding alkyl phenyl selenide.

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