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Letters

Efficient synthesis of diorganyl selenides via cleavage of Se–Se bond of diselenides by indium(III) catalyst and zinc

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Abstract—A simple and efficient procedure for the synthesis of unsymmetrical diorganyl selenides from an one-pot indium(III) catalyzed procedure, in the presence of zinc, has been developed. Various organic halides and even the unreactive organic chlorides underwent the reaction efficiently. Also diaryl and dialkyl diselenides underwent the coupling reaction.

1. Introduction

During the last five decades, selenium compounds have played an important role in organic chemistry, acting as versatile reagents in organic synthesis[1] and catalysis.[2] The biological and medicinal properties of selenium and organoselenium compounds is also increasingly appreciated, mainly due to their antioxidant, antitumor, antimicrobial, and antiviral properties.[3] Besides, the synthesis of peptides containing selenocysteine is rapidly gaining interest with the discovery of an increasing number of proteins containing this amino acid.[4]

The development of new methods for the introduction of selenium-containing groups into organic molecules remains a significant challenge,[5] specially the preparation of unsymmetrical diorganyl selenides.[6] In general, to avoid handling unstable reagents, such as selenols, diorganyl diselenides are used as starting materials and the selenium anion is generated in situ via chemical Se–Se bonds reduction. However, this procedure often requires drastic reaction conditions, such as reduction with hydrides,[7] which reduces the possibility of some functionality or more complex substrates to be present.

On the other hand, indium metal and its salts have been the subject of continued interest because of their remarkable efficiency in various synthetic operations.[8] Particularly, indium(III) halides have found successful applications in synthetic organic chemistry: for example, in ring opening of epoxides and aziridines,[9] Diels–Alder cycloadditions,[10] reductive Friedel–Crafts alkylations[11] or thioacetalization of aldehydes and ketones.[12]

Recently, we reported the synthesis of a new set of chiral α-seleno-amines in a straightforward manner through the stereoselective aziridine ring opening with indium(III)-chalcogenolates, obtained from indium(I) iodide and diorganoyl diselenides.[13] Attempting to disclose further applications of indium salts, we examine here the application of a bimetallic (In(III)/Zn) system, in the generation of selenolate anions. The coupling in situ with organic halides gave the corresponding diorganoyl selenides (Scheme 1).

Our idea was to develop a simple experimental procedure, with a catalytic system easy to handle, less expensive than those with indium(I) and active enough to promote the direct coupling of diselenides and organic halides.[14] The work resulted in an efficient synthesis of diorganyl selenides derivatives under mild and neutral conditions.

The experiments were initially conducted with 1-bromododecane and the phenyl selenolate anion, prepared

$$\mathrm{RSeSeR} \;+\; 2\mathrm{R'X} \xrightarrow[\text{Zn, DMF, 100 °C}]{\text{2.5 - 10 mol \% InX}_3} 2\mathrm{RSeR'}$$

Scheme 1. General synthesis of diorganyl selenides.

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Table 1. In-Catalyzed Zn-mediated reaction of diphenyl diselenide with 1-bromododecane

$$\mathrm{PhSeSePh} + \mathrm{CH_3(CH_2)_{10}CH_2Br} \xrightarrow[\text{Solvent, 1h}]{\mathrm{Zn/\ InX_3}} \mathrm{CH_3(CH_2)_{10}CH_2{-}SePh}$$

Entry	Solvent	InX_3 (mol %)	Yield[a] (%)
1	DMF (100 °C)	$InBr_3$ (10)	100
2	DMF (100 °C)	$InBr_3$ (5)	98
3	DMF (100 °C)	$InBr_3$ (2.5)	98
4	THF (Reflux)	$InBr_3$ (2.5)	25
5	CH_2Cl_2 (Reflux)	$InBr_3$ (2.5)	20
6	CH_3CN (Reflux)	$InBr_3$ (2.5)	30
7	DMF (100 °C)	$InCl_3$ (2.5)	96
8	DMF (100 °C)	$InOTf_3$ (2.5)	94
9	DMF (100 °C)	$InCl_3{\cdot}4H_2O$ (2.5)	88

[a] Yields refer to those of pure isolated products characterized by spectroscopic methods.

through the reaction between PhSeSePh and Zn/InX_3 to establish the best reaction conditions (Table 1). At first, the reaction was carried out with $InBr_3$ (10 mol %) as the catalyst and DMF as the solvent (Table 1, entry 1). Decrease in the catalyst loading from 10 mol % to 2.5 mol %, does not have influence in the reaction, furnishing the corresponding diorganyl selenolate in quantitative yields (Table 1, entries 1–3). Other solvents proved to be less effective for the chemical efficiency of the reaction. Changing the solvent from DMF to THF, CH_2Cl_2 or acetonitrile, causes a drastic decrease in the reaction yield (Table 1, entries 3 vs 4–6). Among the different indium salts tested, it seems to have no influence, since the product was obtained only with a slight decrease in the reaction yield (Table 1, compare entries 3, 7, and 8). However, a significant decrease was observed when $InCl_3{\cdot}4H_2O$ was used (Table 1, entry 9).

Notably, the indium selenolate generated with these bimetallic system (Zn/In(III)) promotes a cleaner and faster reaction than those where the selenolate anion is generated by classic methods. It is worth to mention that these catalytic methods are considered more applicable for preparation of functional unsymmetrical diorganyl selenides because many functional groups cannot withstand the harsh conditions for chemical cleavage of Se–Se bonds.

The mild reaction conditions, its speed and the excellent yields obtained encouraged us to examine the scope and generality of the present method. Various organic halides and different diselenides were then examined for the coupling reaction with the bimetallic system and the results are summarized in Table 2.

In this second set of experiments, various organic halides underwent coupling reaction with diphenyl diselenides in good yileds (Table 2, entries 1–6). As we can see in Table 2, 1-bromobutane and 1-iodobutane efficiently undergo this type of selenilation furnishing the product in 85% and 90%, respectively (Table 2, entries 1 vs 2). Remarkable result was obtained with the unreactive 1-chlorobutane, which furnishes the desired unsymmetrical diorganyl selenide in 83% yield (Table 2, entry 3). Different organic bromides were also used. Allyl and benzyl bromides were converted into their corresponding selenides in excellent yields (Table 2, entries 5 and 6).

It is well known that diaryl diselenides are more reactive than aliphatic ones, and much more easily cleaved. In this way we extended this method to prepare unsymmetrical diorganyl selenides starting from aliphatic diselenides (Table 2, entries 8–12). Applying the same methodology and using dibutyl diselenide as the source for the selenolate anion, the coupling reaction with reactive organic bromides furnishes the desired product in satisfactory yields (Table 2, entries 7 and 8). However, in this case, a longer reaction time was required. Increasing the catalyst loading from 2.5 mol % to 10 mol %, gave a significative improvement on the reaction, affording the unsymmetrical diorganyl selenide in an excellent yield (98%) and with a shorter reaction time (Table 2, entry 9). Also, when the coupling reaction of dibenzil diselenide with organic bromides was carried out, the desired product was obtained in good yields using 10 mol % of $InBr_3$ as the catalyst.

It is well established that zinc metal rapidly inserts into a diselenide bond, and the formed complex $(RSe)_2Zn$ in the presence of a Lewis acids such as $AlCl_3$ or $RuCl_3$ and bromide form the unsymmetrical diorganyl selenide.[15] For the indium(III) catalyzed cleavage of diselenides, a mechanism is proposed as shown in Scheme 2. It starts with the production of di(organylselenyl)zinc **1**, via the insertion of zinc into Se–Se bond. The indium(III) catalyst reacts with **1** to afford the active indium(III) species **2**, which reacts, subsequently, with the organic halide $R'X$, yielding the unsymmetrical diorganyl selenides **3** and species **4**. Moreover, further coupling reaction of **4** with $R'X$ affords **3** and regenerates the catalytic species InX_3. As a consequence, this process enables the consumption of two RSe groups in $(RSe)_2$.

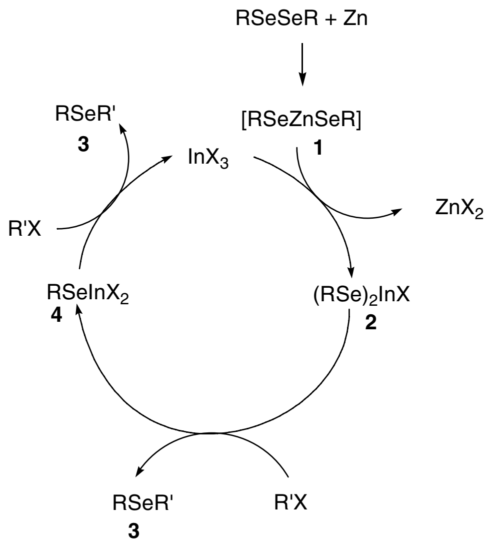
In summary, the present procedure using the bimetallic system (Zn/In(III)) provides a practical straightforward and concise route to a wide range of unsymmetrical diorganyl selenides. These results are similar or even superior, in some cases, to those obtained by using (Zn/Al (III))[15a] or (Zn/Ru (III))[15b] as a bimetallic system. Compared with these others methodologies, the indium(III) catalyzed procedure offers significant

Table 2. Catalytic cleavage of diorganyl diselenides to unsymmetrical diorganyl selenides

$$\text{RSeSeR} + \text{R'Br} \xrightarrow[\text{DMF, 100 °C}]{\text{Zn/ InBr}_3} \text{R'—SeR}$$

Entry	R	Halide	Time (h)	$InBr_3$ (mol %)	Yield[a] (%)
1	Ph	$CH_3CH_2CH_2CH_2Br$	1	2.5	85
2	Ph	$CH_3CH_2CH_2CH_2I$	1	2.5	90
3	Ph	$CH_3CH_2CH_2CH_2Cl$	1	2.5	83
4	Ph	$CH_3(CH_2)_3CH_2Br$	1	2.5	96
5	Ph	$CH_2{=}CHCH_2Br$	1	2.5	82
6	Ph	$PhCH_2Br$	1	2.5	93
7	Bu	$PhCH_2Br$	48	2.5	58
8	Bu	$CH_3(CH_2)_{10}CH_2Br$	48	2.5	67
9	Bu	$CH_3(CH_2)_{10}CH_2Br$	22	10	98
10	$PhCH_2$	$PhCH_2Br$	72	2.5	22
11	$PhCH_2$	$PhCH_2Br$	48	10	58
12	$PhCH_2$	$CH_3(CH_2)_{10}CH_2Br$	22	10	57

[a] Yields refer to those of pure isolated products characterized by spectroscopic methods.



Scheme 2. Assumed catalytic cycle.

improvements with regards to operational simplicity, reaction times and high isolated yields of products. Organic halides, such as unreactive chlorides, and aryl or alkyl diselenides can be used for the coupling reaction under mild conditions.

A typical experimental procedure is as follows: To a stirred solution of appropriate diselenide (0.5 mmol), zinc powder (0.8 mmol, 0.0523 g), indium tribromide (2.5 mol %) in DMF (3 mL), under an argon atmosphere, was added the alkyl, allyl or benzyl bromide (1.2 mmol) and the mixture heated up (100 °C) for the time indicated in the Table 2. After this time the reaction mixture was cooled to room temperature, quenched with water (10 mL) and extracted with ether (3 × 15 mL). The combined ether extract was washed with brine, dried (Na_2SO_4), and filtered through a plug of Celite. The solvent was removed to leave the crude product, which was purified by column chromatography over silica gel using hexane as solvent.

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