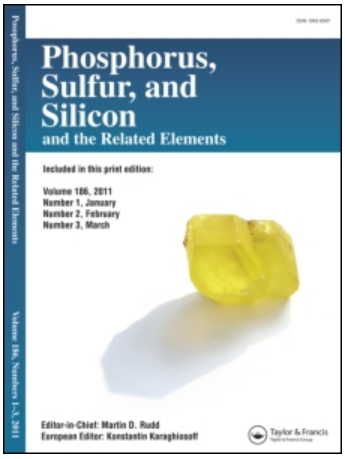

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Synthesis of Chalcogenides using Indium Intermediates in Aqueous Media

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Selenides and vinylic selenides were synthesized from their corresponding organic halides and alkynes in aqueous media using indium metal.

Keywords: chalcogenides; indium; aqueous media

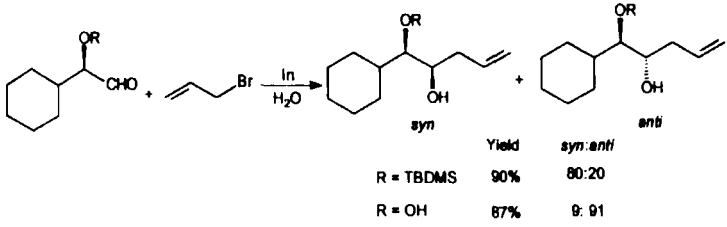
The importance of organometallic reactions in organic synthesis is well known[1]. Since the discovery of the formation of alkylzinc compounds by Frankland from iodoalkanes and metallic zinc[2], the importance of organometallic reagents for synthetic purposes has been growing, specially in building new carbon-carbon bonds that leads to compounds of greater complexity.

More recently, organometallic type reactions in aqueous media have attracted considerable interest in organic synthesis[3]. The idea of performing organometallic reactions using water as solvent seems *unconventional* because the classic organometallic reactions like Reformatzky[4], Barbier[5], Grignard[6] and Gilman,[7] are sensitive to moisture and when generated, the organometallic compound must avoid the presence of water. In this way, the carbon-carbon bond formation in aqueous media has been limited to electrochemical processes[8] and aldol condensation reactions[9]. However, some classes of organometallic compounds remain viable in the presence of water[10,11]. Such reactions offer several advantages: (a) anhydrous solvents are not required; (b) protection and deprotection steps are avoided; (c) water soluble compounds can be used directly without derivatization (i.e. carbohydrates); (d) some changes in the chemo- and stereoselectivity can be observed and (e) the environmental benefits.

Significant progresses have been made showing that organometallic reactions can be carried out in aqueous medium through a variety of metal mediators like zinc[12], tin[13], indium[14] and bismuth[15].

Indium organometallic compounds were found to work efficiently with a variety of reactants[16]. Unlike other metal analogs, which very often require acid catalysts, heat or sonication to promote the reaction, indium organometallics can be easily generated in water or combinations of water and miscible solvents, without any additive. The exceptional stability to air and water compared to other metals, the unusual reactivity and theirs easy preparation, have attracted the attention to the chemistry of indium compounds. In fact, indium was

found to work effectively in a variety of reactions. For example, the reaction of α-alcoxyaldehydes with allyl bromide promoted by indium in water, yield preferentially the *anti* product[17]. However, the allylation of α-hydroxyaldehydes using the same procedure yield the *syn* isomer as the major product (SCHEME 1).



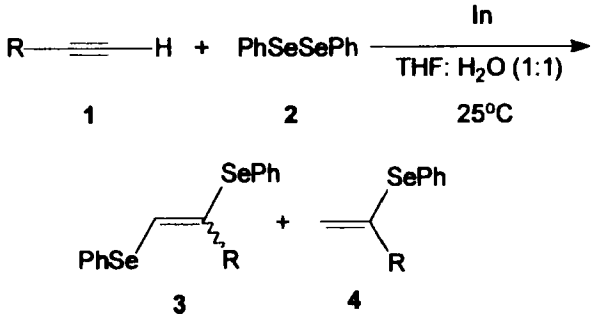
SCHEME 1

Other interesting reactions like reductive coupling of aldimines[18], Reformatsky and aldol type reactions[19], allenylation of aldehydes[20], ring expansions[21], Michael additions[22], stereoselective debromination[23] and pinacol coupling[24] can be performed by indium intermediates in water.

Vinylic chalcogenides are compounds widely described and an impressive number of publications dealing with this subject have appeared in the literature in the last years[25]. Most of the methodologies described to obtain this class of compounds are mainly based on the addition of nucleophilic[26] or electrophilic[27] chalcogenide species to the carbon-carbon triple bond as well as on free radical mechanism reactions[28].

Particularly, of our interest, is the synthesis of 1,2-bis-(phenylseleno) alkenes. The methods described to obtain these compounds are mainly based on the addition of phenylseleno radical to alkenes and alkynes[29]. It is well known that organic dichalcogenides undergo photolysis to generate the corresponding thio- and selenoradical as labile species[30]. However, these chalcogen atom-centered radicals are less reactive toward the carbon-carbon unsaturated bonds being more liable to recombine and reform the dichalcogenides. Consequently, the corresponding addition products are obtained in low yields.

Other methodologies based on the addition of diphenyl diselenides to terminal alkynes catalysed by tetrakis (triphenylphosphine) palladium(0), yields the corresponding 1,2-bis(phenylseleno) alkenes with Z stereochemistry[31, 32] Recently, we described our preliminary results for the synthesis of 1,2-bis(phenylseleno) alkenes **3**, starting from terminal alkynes **1** and diphenyl diselenides **2** promoted by indium metal in aqueous conditions (SCHEME 2, Table 1).



SCHEME 2

It is known from literature that the reaction of indium metal with allylic halides performed in water, proceeded faster than those in THF. However, a 1:1 mixture of the two appeared to be optimal, presumably, by increasing the solubility of the halide component. In analogy, the reaction was carried out using a THF: H_2O (1:1) system as solvent at room temperature. Diphenyl diselenide was added to a suspension in THF:H_2O of indium metal divided in small pieces, followed by the addition of the appropriate alkyne.

TABLE 1: Reaction of terminal acetylenes **1** with diphenyldiselenide **2** promoted by metallic indium

R	Ratio 3:4	Yield [a,b] (3+4)%
n-Bu	18:82	50
Ph	90:40	50
CO_2Et	83:17	85
CH_2OTHP	33:77	52
$CH_2OTBDMS$	40:60	50

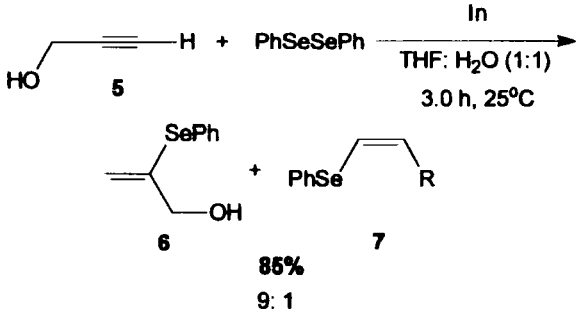
a. Chromatographic GC yield.

b. All compounds exhibit NMR, Mass and combustion data according with their structures.

We obtained a mixture of 1,2-bis(phenylseleno) isomer **3** and the 1,1-(phenylseleno) isomer **4** in moderate yields and its ratio was determined by ^1H NMR and GC.

An exception occurred when propargylic alcohol **5** was used as the alkyne source. In this case, the main product obtained was the 1,1-

isomer **6**, together with a small amount of the Z-1,2-isomer **7** (SCHEME 3).



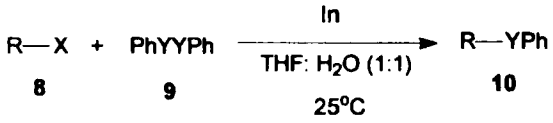
SCHEME 3

This methodology can be a useful preparation for 1,1-disubstituted vinylic selenides and complements the procedures already described for the preparation of this class of compounds[33].

Organic chalcogenides have also been recognised as useful *synthons* in organic synthesis and its chemistry is well known. Several transformations which allow the presence of functions, masked and protected groups as well as multiple bonds, can be performed by these compounds. Most of the methodologies described to obtain selenides are mainly based on the use of arenediazonium salts[34]; electrophilic selenium species[35], reduction of dichalcogenides[36] and the reaction with organometallic reagents[37]. More recently, some new methodologies dealing with allylation and propargylation reactions with metals in aqueous media, have appeared in the literature[38].

We have found that selenides **10**, can also be synthesised by the simple mixture of the appropriate organo halides **8**, and diphenyl dichalcogenides **9** mediated by metallic indium using THF:H_2O as

solvent in good yields. The reaction occurred smoothly and no side products were detected (SCHEME 4, TABLE 2)



SCHEME 4

TABLE 2: Reaction of organo halides **8** with diphenyldichalcogenides **9** promoted by indium metal

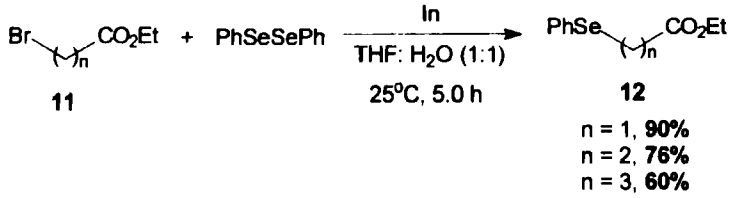
R	X	Y	Reaction Time (h)	Yield [a,b] (%)
Me	I	Se	4	97
n-Bu	Br	Se	24	74
n-Bu	Br	S	24	65
t-Bu	I	Se	24	51
$PhCH_2$	Br	S	24	70
$PhCH_2$	Cl	Se	4	45
$PhCH_2$	Br	Se	24	98
$HC{\equiv}CCH_2$	Br	Se	24	12
$PhCH{=}CH_2$	Br	Se	24	60

a. Chromatographic GC yield.

b. All compounds exhibit NMR, Mass and combustion data according to their structures.

When phenyl- and vinyl halides were used as starting material, the products were obtained in low yields, demonstrating some limitations of the methodology. However, this reaction is still an interesting synthetic tool over the existing methodologies once it can be performed in water just by mixing the starting materials.

Despite the existence of similar methodologies to the synthesis of α-selenocarbonyl compounds **12**[39], the procedure we described above proved also to be useful for preparing the β and γ derivatives in good yields by using the same reaction conditions and the corresponding α–, β– or γ-halocarbonyl compounds **11** and metallic indium (SCHEME 5).



SCHEME 5

The exact mechanism for these reactions is unknown. Different authors have proposed three different mechanisms to explain these metal mediated reactions. The first one is based in a free radical process[40], the second in a radical anion[41] one and more recently a new mechanism-pathway based on the reaction of a pre-formed metal reagent, was described[42].

The triad suggested by Li and Chan is a useful tool for understanding the operating mechanism[43]. It could be located

anywhere within the triad, while the exact location is determined by the reaction substrate, metal used and the reaction conditions (FIGURE 1).

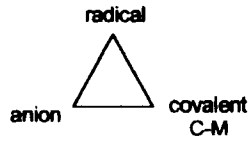


FIGURE 1: The Triad Reaction Mechanism

In conclusion, the methodology described for the preparation of chalcogenides mediated by elemental indium in aqueous media approves to be a good and efficient alternative procedure, due to its technical simplicity, smooth conditions and good yields.

EXPERIMENTAL

Preparation of compounds 3 and 4

To a round bottom flask containing a suspension of indium metal (1.0 mmol, 0.114 g) [divided in small pieces] in a mixture of THF:H_2O (1:1)(2.0 mL) was added diphenyldiselenide (1.0 mmol, 0.312g) followed by the appropriate alkyne (2.3 mmol). The reaction was stirred for the time indicated in Table 1 and then quenched by the addition of brine and extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified by a silica gel chromatographic column using hexane as eluent.

Preparation of organochalcogen compounds **10**

To a round bottom flask containing a suspension of indium metal (1.0 mmol, 0.114g) [divided in small pieces] in a mixture of THF:H_2O (1:1)(2.0 mL) was added the diphenyldichalcogenide (0. 5 mmol) followed by the appropriate organic halide (1.0 mmol). The reaction was stirred for the time indicated in Table 2 and then quenched by the addition of brine and extracted with ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate. The solvent was evaporated and the residue was purified by a silica gel chromatographic column using hexane as eluent. The same procedure was used for the preparation of α-selenocarbonyl compounds **12**.

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