Zinc-Mediated Synthesis of Vinyl Selenide and GPx-like activity

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Abstract

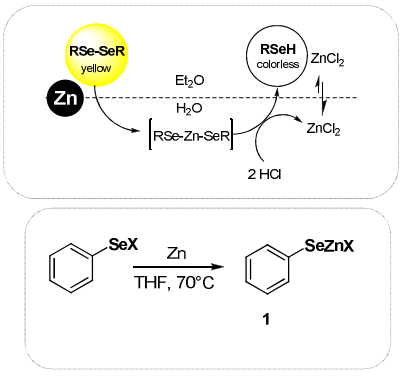
Phenyl selenol and the zinc-selenolate PhSeZnCl can be conveniently employed for the stereospecific and stereoselective synthesis of vinyl selenides. These reactions occur with moderate to high yields and can be accomplished in eco-compatible conditions using a biphasic acidic system or directly an aqueous suspension.

Introduction

Vinyl selenides are intermediates of great synthetic interest, and their versatility in organic synthesis has been widely documented.[1] They combine the functional transformations achieved by the well-known reactions of organoselenium compounds (e.g. selenoxides, *syn* elimination) with the ability of carbon–carbon bond-forming reactions involving the double bond, associated with the ability of selenium to stabilize adjacent positive and negative charges.

Phenylselenol and selenolate are convenient organoselenium reagent and their role in effecting many synthetic transformations is well known. Even if a number of procedures for the *in situ* generation of these species have been reported,[2] most of them suffer from serious drawbacks such as bad smelling, moisture sensitivity, strong basic reaction conditions, use of hazardous organic solvents. In order to overcome these drawback and look for more eco-sustainable strategy to perform organic reaction, recently, we introduced two new procedures using zinc as reducing agent in the preparation of selenols[3] and selenolates[4] starting from diselenides and phenylselenyl halides, respectively. We reported that zinc shavings in a 1:1 mixture of 0.18 N HCl/ Et_2O at 20°C reduces diselenides affording the corresponding selenols which can be isolated or directly treated with different nucleophiles.[3] In a different way the ttreatment of commercially available PhSeCl with a stoichiometric amount of zinc powder in refluxing THF leads to the corresponding solid and air-stable zinc selenolate **1** through an oxidative insertion of zinc into the selenium–chlorine bond (Scheme 1).[4]

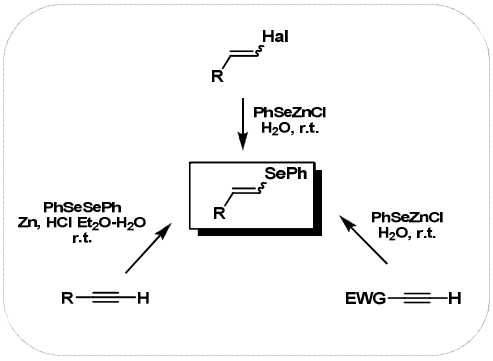
Scheme 1. Zinc-mediated synthesis of selenols and selenolates



Results and Discussion

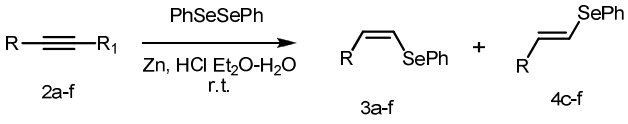
We now report that these procedures can be conveniently employed to effect the synthesis of vinyl selenides in "on water condition" or using a biphasic acidic system, starting from vinyl halides or substituted alkynes (Scheme 2).

Scheme 2. Strategies used for the vinyl selenides synthesis



The hydroxiselenenylation of alkynes shows high stereoselectivity affording mainly the Z-isomer. The double bond geometry was determined by ^1H NMR spettroscopy and for the **3e** and **4e** products by the n.O.e. correlation (Table 1).

Table 1. Hydroselenation of alkynes

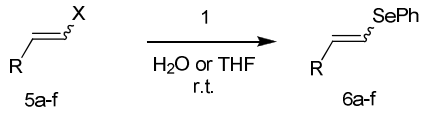


Entry	R	R_1	T(h)	Yield %	Z/E
2a	Ph	H	24	68	100:0
2b	COOEt	H	24	70	100:0
2c	*p*-Br-Ph	H	24	60	91:9
2d	*p*-MeO-Ph	H	24	48	24:76
2e	Ph	COOMe	24	70	72:28
2f	Tyophen-2-yl	H	24	80	85:15

Vinyl selenides have been also achieved by nucleophilic substitution on vinyl halides. These reactions were performed both in THF solution both in water suspension and in this latter case the reactions

resulted faster (Table 2). Detailed ^{1}H and ^{13}C NMR analyses of products **6a-f** and of the corresponding crude mixtures indicated the stereospecific (**6a, 6b, 6e** and **6f**) and the stereselective (**6c**) formation of one stereoisomer depending on the geometry and the substituents on the double bond. In all the cases, except the ketone ***(E)*-6c**, derivates from ***(Z)*-5c** and ***(E)*-5d**, a geometry retention was observed. DFT calculation have been performed on a model system in order to enlighten the reaction mechanism that seems to be influenced by the preservation of a strongly stabilizing Se-Zn interaction.

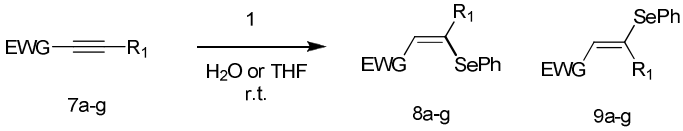
Table 2. Nucleophilic substitution on vinyl halides



Entry	R	X	Yield H_2O (2h)	*Z*/*E* (H_2O)	Yield THF (24h)	*Z*/*E* (THF)
***(Z)*-5a**	Ph	H	83%	100:0	68%	100:0
***(E)*-5b**	Ph	H	94%	0:100	70%	100:0
***(Z)*-5c**	PhCO	H	85%	95:5	60%	91:9
***(E)*-5d**	PhCO	H	99%	81:19	48%	24:76
***(Z)*-5e**	EtOOC	COOMe	70%	100:0	70%	72:28
5f	4-Chloro-3-nitrocumarine	H	78%	--	80%	85:15

A Michael Type reaction of zinc-selenolate **1** on activated triple bonds represent another usefull strategy for the regio- and stereoselective synthesis of funtionalyzed vinyl selenide (Table 3). The resulting alkene because of the presence of a –SePh group resulted unable to give a further addition. Also in this case the reactions performed in "on water" conditions proceed faster and the nature of the electron-withdrawing group seems to have no influence on the course of the reaction.

Table 3. Michael-type addition on alkynes

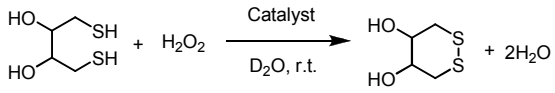


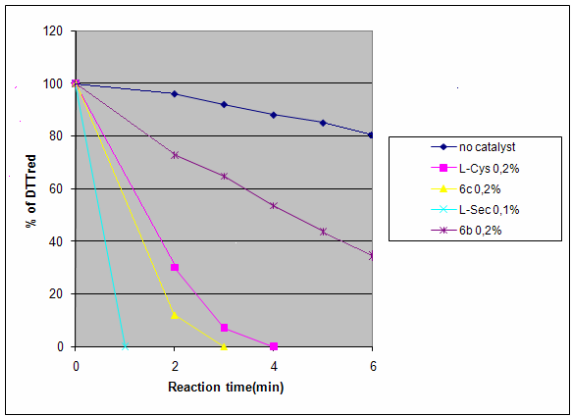
Entry	EWG	R_1	Yield H_2O (2h)	*Z*/*E* (H_2O)	Yield THF (24h)	*Z*/*E* (THF)
7a	MeOOC	H	99%	100:0	99%	85:15
7b	PhCO	H	85%	79:21	90%	87:13
7c	MeCO	Ph	99%	65:35	50%	83:17
7d	$C_5H_{11}CO$	H	99%	75:25	93%	85:15
7e	MeOOC	Ph	99%	75:25	--	--
7f	HOOC	Ph	--	--	--	--
7g	CHO	C_5H_{11}	83%	80:20	93%	80:20

GPx like activity

After the observation that ebselen mimics the catalytic action of the Glutathione Peroxidase, several research groups have been interested in identifying efficient and simple GPx-mimics in order to develop new drugs able to protect cells against oxidative stress. We tested some vinyl selenides and other organoselenium compounds, using *in vitro* ^{1}H-NMR experiments based on the interconversion reaction between thiols and disulfides in presence of stoichiometric amounts of hydrogen peroxide (Scheme 3).[5] In the graph we compared this results with those obtained from cysteine and vinyl selenides **6b** and **6c**.

Scheme 1. GPx-like activity test





In the absence of the catalyst, 66% of DTT^{red} remained unreacted after 15 min. In contrast, the oxidation reaction was completed in 1 min using L-Selenocystine, the actual amino acid located into the active site of the enzyme. Both 6c and 6b showed to be slower catalyst than L-Sec but similar or even faster than the L-Cys. Further vinyl selenides are under investigation.

Conclusion

In conclusion we present here three different and conveniently strategies for the synthesis of vinyl selenides. These procedures offer significant advantages with regards to operation and yields and thus presents an efficient alternative to the existing methods. Finally, the described procedures demonstrate the synthetic utility of the PhSeZnCl as nucleophilic organoselenium reagent.

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