Vinylic Substitutions Promoted by PhSeZnCl: Synthetic and Theoretical Investigations

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Vinyl selenides can be easily obtained through nucleophilic substitution of the corresponding halides by using PhSeZnCl in THF as well as "on water" conditions. The reaction is stereospecific with retention of the alkene geometry. The only exception has been observed in the reaction conducted on a β -chloro- α , β -unsaturated ketone, which afforded the (*Z*)

product starting from either the (E) or (Z) isomer. DFT calculations have been performed in order to investigate the reaction mechanism, the stereochemistry of the process and the role of the zinc atom.

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Here we report that **1** can be used for the synthesis of vinylic selenides starting from the corresponding halides. Many vinylic sulfide, selenide and telluride preparations in-

volve the use of expensive catalysts or not readily available

Introduction

Phenyl selenolate is one of the most convenient organoselenium reagents, and its role in effecting many synthetic transformation is known.^[1] A number of procedures for the "in situ" generation of selenolates have been reported,^[2] but most of them suffer from serious drawbacks such as bad smelling, moisture sensitivity, strong basic reaction conditions, use of hazardous organic solvents. Recently, the use of zinc as reducing agent for the preparation of selenols was reported,^[3] and we demonstrated that treatment 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^[4] (Figure 1).



Figure 1. Bench-stable selenolate PhSeZnCl (1).

This reagent has been efficiently employed in the ring opening of epoxides, and we reported also an unexpected rate acceleration when these reactions were effected by "on water" conditions.^[5]

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starting materials.^[6] Moreover, often the products are obtained as mixtures of regio- or stereoisomers. Vinylic selenides are intermediates of great synthetic interest, and their versatility in organic synthesis is well documented through the publication of a number of reviews and books.^[6b,7] 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 capacity of selenium to stabilize adjacent positive and negative charges (Scheme 1).



Scheme 1. Vinylic selenides as useful synthetic intermediates.

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A serious drawback that prevents the preparation on a large scale and the use in organic synthesis of vinylic selenides is the lack of simple and efficient methods for their preparation. We considered vinylic halides as easy and inexpensive starting materials, since many methods are available for their diastereoselective preparation.^[8]

Results and Discussion

The starting vinylic halides 2a,g used in the present investigation are commercially available or were prepared according to literature procedures.^[9] With these compounds in hand we started the study by treating the halide 2a with PhSeZnCl (1) at 25 °C in THF as well as under "on water" conditions at the same temperature. As already observed for the ring opening of epoxides, a rate acceleration under "on water" conditions has also been observed in this case. Under the latter conditions the starting material was almost quantitatively consumed after 2 h, whereas in THF solution the reaction was stopped after 24 h. After determining the best experimental conditions for the vinylic substitution reaction, a more detailed study was performed by treating a series of functionalized halides 2a-f with 1 (Scheme 2, Table 1). Detailed ¹H and ¹³C NMR analyses of products 3a-f and of the corresponding crude mixtures indicated the stereospecific (3a, 3b, 3e, 3f) or stereoselective (3c) formation of one stereoisomer depending on the geometry and the substituents on the double bond.



Scheme 2. Vinylic substitution of halides.

In all the cases, with the only exception of ketone (E)-2d that leads mainly to the formation of selenide (Z)-3c, a geometry retention was observed. Interestingly the reaction performed starting from the dibromide 2g affords quantitatively the product deriving from the nucleophilic substitution only at the aliphatic carbon atom, even in the presence of 2.2 equiv. of PhSeZnCl (1; Scheme 3). This clearly indicates that non-activated vinylic halides are almost unreactive toward substitution both in water and THF.

The mechanism of vinylic nucleophilic substitutions has received considerable attention in the last 40 years.^[10] Many mechanistic variants have been found for this reaction, ranging from a single-step in-plane substitution, affording the products stereospecifically with inversion of the configuration, to a multi-step process in which the nucleophile attacks the alkene on the π^* orbital giving a tetrahedral intermediate. The fate of the latter depends especially on the nature of the leaving group: if it is a poor nucleofuge a rotation about the C_{α} – C_{β} bond can occur leading to stereoconvergence. The course of the transformation, however, depends on several factors such as the nucleophile and the





[a] (Z)/(E) ratio = 95:5. [b] (Z)/(E) ratio = 91:9. [c] (Z)/(E) ratio = 81:19.



Scheme 3. Chemoselectivity investigation.

leaving group, the solvent and the substituents on the olefin (particularly the presence and the nature of electron-withdrawing groups). For this reason we believe that any general argumentation on this topic can be oversimplifying and misleading. Since nucleophilic vinylic substitutions with selenium nucleophiles have never been studied by computational methods and by considering the singularities of our system, i.e. the presence of zinc, we decided to undertake a mechanistic study by means of DFT calculations (see Supporting Information for details). In particular, we considered that in our case the reaction can be significantly influenced by the presence of Zn–O and Zn–Se interactions.

We focused our attention on the substitution of the two isomers of 3-chloro-1-phenylprop-2-en-1-one (2c,d), the only example in which both the isomers lead to the (Z)-1phenyl-3-(phenylseleno)prop-2-en-1-one (3c). However, due to limitations in computational resources we decided to use a model system in which both the phenyl rings of substrate and nucleophile are replaced by methyl groups (Scheme 4).



Scheme 4. Model system for computational study.



Figure 2. Free-energy profile for the vinylic substitution on (Z)-A. The black lines represent the gas-phase reaction, the grey lines include the solvation contributions in tetrahydrofuran (see Supporting Information for details).

First, we focused our attention on the reaction on (Z)-A (Figure 2). After the exergonic formation of a substrate– nucleophile complex, the attack of the nucleophilic selenium atom occurs perpendicular to the olefin plane leading to tetrahedral intermediate **E**.

An early transition state (**TS2**) allows the elimination of the chlorine atom and the formation of the product (*Z*)-**C**. Two possible mechanisms can be envisioned for the formation of the (*E*) product: (a) the elimination of the chlorine atom occurs after a rotation of the C_{α} - C_{β} bond; (b) a single-step $S_N V \sigma$ reaction in which the nucleophile attacks at the σ^* orbital of the C–Cl bond. Transition states have been found for both possibilities. The transition state for the rotation (**TS3**) leading to a possible formation of the product (*E*)-C has an activation energy significantly higher than the virtual no barrier found for the elimination leading to (*Z*)-C (**TS2**) ($E_a = 15.5$ vs. 1.4 kcal/mol in the gas phase and 15.4 vs. 1.0 kcal/mol in THF). The transition state for the S_NV σ mechanism has a prohibitively high activation energy ($E_a = 42.4$ kcal/mol in the gas phase and 41.5 kcal/mol in THF), and thus this mechanism can be reasonably excluded. The mechanism of the reaction on the substrate (*E*)-A is similar (Figure 3). The nucleophile attacks the substrate at the π^* orbital to afford a tetrahedral intermediate F. This can then turn in the intermediate E, passing through low-activation-energy transition states **TS6** and **TS7** and intermediate G. This process seems to be energetically favored by the preservation of a strongly stabilizing Se–Zn interaction.



Reaction coordinate

Figure 3. Free-energy profile for the vinylic substitution on (E)-A. The black lines represent the gas-phase reaction, the grey lines include the solvation contributions in tetrahydrofuran (see Supporting Information for details).

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Figure 4. Transition states and structures of intermediates. Distances are in Å, relative free energies in kcal/mol. Values in parentheses include the solvation contributions in tetrahydrofuran.

Intermediate E, as already found in the mechanism of the substitution of the (Z) substrate, can afford the experimentally most abundant product (Z)-C by passing through TS2. Also in this case a transition state (TS9) for an $S_N V \sigma$ mechanism, leading to the same product, has been found, but the extremely high activation energy ($E_a = 47.0$ kcal/ mol in the gas phase and 46.0 kcal/mol in THF) discards any possibility of this mechanism to occur. The formation of a small amount of (E)-C can be explained by rotation about the C_{α} - C_{β} bond leading to a structure with the selenium moiety in a *trans* relationship to the carbonyl group. A transition state (TS8) relative to this rotation has been found, but again the activation energy is considerably higher than the one relative to the rotation leading to (Z)-C ($\Delta E_a = 11.5$ kcal/mol in the gas phase and 12.2 kcal/mol in THF) (Figure 4).

Conclusions

We reported the first study of nucleophilic vinylic substitution of a zinc selenolate on vinylic halides by using "on water" conditions. The reaction mechanisms of a β -chloro- α,β -unsaturated ketone has been computationally investigated on a model system. The preferential formation of the (Z) product both when the reaction is performed on the (Z) and on the (E) substrate has been explained in terms of relative activation energies. The contribution of the solvent has been considered but it has been found to be irrelevant. Finally, these results suggest that the outcome of the reaction is strongly influenced by the presence of zinc.

Experimental Section

General Procedure for the Reactions Effected in THF: To a solution of 1 (1.0 mmol) in THF (3 mL), under anhydrous conditions, 1.0 mmol of the vinylic halide 2a-g dissolved in THF (2 mL) was added. The resulting mixture was stirred at room temperature for 24 h, and the reaction progress was monitored by TLC and GC-MS. The reaction mixture was then poured into water and extracted three times with CH₂Cl₂. The combined organic layers were dried with Na₂SO₄, filtered, and the solvent was removed under vacuum. The product was purified by flash chromatography. The yields reported in Table 1 refer to isolated products.

General Procedure for the Reactions Effected under "On Water" Conditions: 1.0 mmol of 1 and 1.0 mmol of the vinylic halide 2a-g were poured into 6 mL of water and vigorously stirred at room temperature for 2 h. Then the water was extracted three times with CH_2Cl_2 . The combined organic layers were dried with Na_2SO_4 , filtered, and the solvent was removed under vacuum. The product was purified by flash chromatography. The yields reported in Table 1 refer to isolated products.

Supporting Information (see footnote on the first page of this article): Detailed experimental procedures, spectroscopic data of new compounds, computational details and cartesian coordinates for all optimized stationary points and transition states.

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