

Efficient Eco-Friendly Solvent-Free obtaining Bis-selenium-alkenes with High Biological Potential †

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Abstract: Organocalcogenides, in particular, organoselenium compounds have been widely studied due to the large number of synthetic and biological applications. Among organoselenium compounds, a class of bis-selenide-alkene derivatives has attracted attention. Recently, some studies have been developed to the synthesis of vinyl chalcogen derivatives, since these are also highly valuable intermediates in several synthetic applications. However, the methodologies developed so far have extensive reaction times, use of toxic solvents and heavy metals. Therefore, there is an emerging need to develop protocols for the synthesis of these molecules that are in accordance with the principles of green chemistry. In this work, we developed an alternative synthesis of bis-selenium-alkene derivatives, through an environmentally appropriate methodology. Reaction optimization was evaluated from the diphenylacetylene and diphenyl diselenide, using I₂/DMSO as a catalytic system under microwave irradiation or conventional heating. The variations of these conditions were carried out through different equivalences between the reagents, the amount of catalyst (I₂), temperature, DMSO and the reaction process (MW or conventional). Even now, it was found that the best established condition was using diphenylacetylene, diphenyl diselenide, 30mol% I₂ in DMSO, under microwave irradiation at 100°C for 10min. In this condition the product was obtained in 82% yield and its characterization was performed using ¹H and ¹³C NMR spectroscopy. Therefore, the methodology that is being developed, in addition to perfectly attending to the principles of green chemistry, will allow to evaluate the reaction scope using different alkenes and diselenides or even disulfides and ditellurides.

Keywords: catalysis; green chemistry; environment; synthesis

1. Introduction

In recent years, organoselenium compounds have shown extensive academic interest because of their broad biological activity, just as pharmacological actions [1]. An important example of this class of compounds is ebselen (Figure 1), which recently stood out for being promising, among 10,000 substances studied, in the treatment against COVID-19. [2] Among organoselenium compounds, a class of di- and tri selenide alkene derivatives have received great attention in recent decades, due to their chemical properties and, also, great pharmaceutical potential [3]. Besides that, the interest in the chemistry of bis-vinyl-selenides has increased since their important functionality was discovered as valuable intermediates, with considerable synthetic application. So, there are numerous advantages for this class of compounds, among them, can be highlighted its potential in synthetic applications. The diverse applicability of this type of molecules can be explained by the fact that the chalcogen atom exerts a stabilizing effect on positive or negative neighboring charges that makes the double bond in

vinyl chalcogenides susceptible of both nucleophilic and electrophilic attacks, an extremely useful resource for organic synthetic purposes.

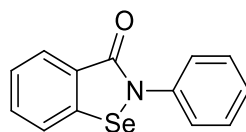
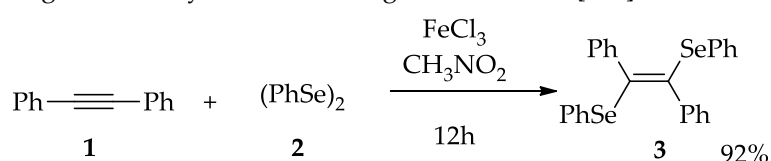


Figure 1. Ebselen structure.

However, despite the fact that bis-vinyl-selenides compounds are very promising in biological and synthetic aspects, the methods applied until now for their synthesis are considerably outdated and aggressive from an environmental point of view. As can be seen in scheme 1, the obtaining of this type of structure was carried out through a methodology with several disadvantages, such as the use of toxic solvents, reagents, heavy metals and long reaction times [4–6].



Scheme 1. Bis-selenide-vinyl obtaining in previous work [4].

Therefore, due to the importance of these class of organoselenium compounds, there is a growing need for the development of environmentally accepted protocols. In this work it is proposed a new environmentally friendly methodology for synthesis of bis-selenide-alkene derivatives using the green catalytic system I_2 / DMSO.

2. Methods

General procedure for the synthesis of bis-selenide-alkene derivatives. In a specific microwave glass tube (10 mL) equipped with a magnetic stir bar, diphenylacetylene (0.125 mmol), diphenyl diselenide (1 eq.), I_2 (30mol%) and DMSO (2 eq.). Then, the tube was sealed with an appropriate cap and the reaction mixture was placed in the microwave reactor, in a closed system, and the power conditions (100 W), temperature (100 °C), time (20 min) and heating ramp (1 min). The reaction system was irradiated at maximum power until reaching the programmed temperature, for 20 min. After reaching the programmed temperature, the device was adjusted to keep the temperature constant. After the completion of the reaction, 5 mL of ethyl acetate (AcOEt) was added and the reaction mixture was washed with 10% $\text{Na}_2\text{S}_2\text{O}_4$ solution. The crude product was purified by preparative plate, eluting with a hexane.

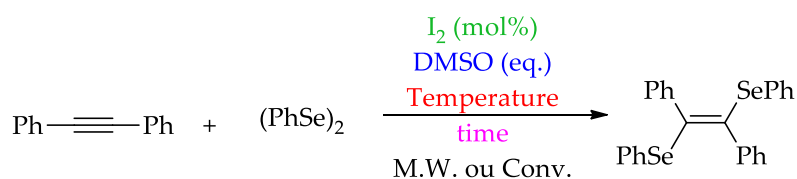
Characterization. *1,4-diphenylethyne* (Compound 3). 0.027 g, Yield: 82%, brown-yellow white oil, ^1H NMR (500 MHz, CDCl_3) δ 7.98 (d, J = 10 Hz, 1H), 7.66 (t, J = 5Hz, 10H), 7.51 (t, J = 5Hz, 10H).

3. Results and Discussion

According to the objectives proposed for this work, the reaction between diphenylacetylene (1) and $(\text{PhSe})_2$ (2) was used as a standard reagent to optimize the reaction parameters. As observed in the results showed in Table 1, the first reaction with 1 eq. of (2), 1 eq. DMSO, 10mol% of I_2 was performed under conventional heating at 100 °C for 24 h. In this condition the desired product 3 was obtained in 20% of yield (Table 1, entry 1). Then, the reaction time was increased and the bis-selenide-alkene (3) was achieved only in 15% of yield (Table 1, entry 2). Using the same quantities of the reagents and same temperature, the reaction was performed under microwave irradiation during 20 min and the yield obtained was 17% (Table 1, entry 3). Entries 3 and 4, when the amounts of iodine and DMSO are varied, there was an increase in the yield. Encouraged by this result, the next parameter analyzed was the $(\text{PhSe})_2$ (2) equivalents and, for our delight, according to entry 6, 0.55

eq. of (2) causing a jump in the reaction yield value to 82%. Then, it was evaluated a shorter reaction time and the product formed with 70% of yield.

Table 1. Reaction optimization reactions.



#	(PhSe) ₂ (eq.)	DMSO (eq.)	I ₂ (mol%)	T (°C)	Time	Reaction process	Yield(%)
1	1	1	10	100	24 h	conventional	20
2	1	1	10	100	64 h	conventional	15
3	1	1	10	100	20 min	microwave	17
4	1	1	30	100	20 min	microwave	33
5	1	2	30	100	20 min	microwave	30
6	0.55	2	30	100	20 min	microwave	82
7	0.55	2	30	100	10 min	microwave	70

As an example, the product of interest (3) was characterized by analysis of hydrogen nuclear magnetic resonance (500 MHz, CDCl₃). In this spectrum shown in Figure 2, it is possible to observe at 7.98 ppm the presence of a doublet (J = 10Hz) sign with integral relative to 8 aromatic hydrogens. At 7.66 ppm there is a triplet (J = 5Hz, 10Hz) with integral relative to 4 aromatic hydrogens. Finally, at 7.52 ppm is located another triplet (J = 5Hz, 10Hz) referring to the other 8 aromatic hydrogens that make up the molecule, that total the expected hydrogens for the molecule.

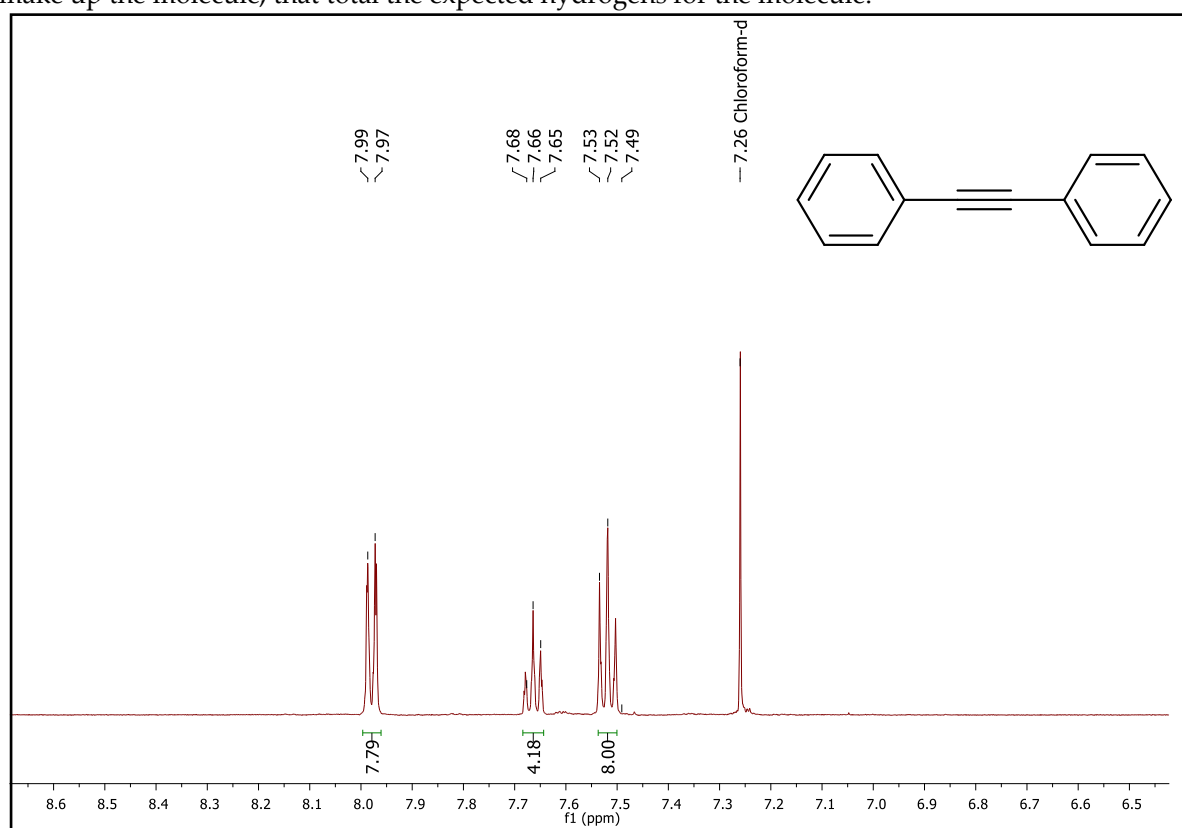


Figure 2. ¹H-NMR spectrum of compound 3.

It is important to highlighted that this work is in process. It will be necessary to evaluate more reaction parameters, such as the reaction time, to have the condition optimized. However, since

March so far it has not been possible to proceed due to the arrival of the Covid-19 Pandemic and the suspension of the laboratory activities in the University.

4. Conclusion and Perspectives

The present work has shown, so far, that the methodology is being optimized in an effective and satisfactory way, enabling the formation of the desired bis-selenide-alkene **3** in high yield (82%). The methodology follows the principles of green chemistry without using solvent, heavy metals and long reaction times. As soon as it is possible to return to post-pandemic activities, it is intended to proceed with the optimization steps by varying more the diselenide equivalents, DMSO and also the reaction temperature, time. Therefore, after the establishment of an optimized methodology, the reaction scope will be evaluated using different substituted diselenides and even disulfides or ditellurides.

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