

I₂-Catalyzed/DMSO System for the Oxidation of Se-Se Bond Activated by the Use of SynLED Parallel Photoreactor[®] †

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Abstract: Among the different green oxidative protocols, I₂-catalyzed/DMSO systems have recently received considerable attention due to being greener, efficient, atom-economical, low-cost, and offering the possibility to perform reactions under safe and mild conditions. Of particular interest is their application in the chalcogen–chalcogen bond activation that allows for the in situ formation of electrophilic species, promoting the formation of a number of Se-C bonds. Iodine acts as a catalytic oxidant in these reactions and is continuously regenerated by the DMSO, which can be used in stoichiometric amounts under solvent-free conditions. Methoxyselenylation reactions can be performed at room temperature; however, the reaction takes over 24 h to reach appreciable conversion yields. In this paper, activation by the use of a SynLED Parallel Photoreactor[®] is investigated as an alternative energy source, and the results are critically compared with those previously reported in literature.

Keywords: photoreaction; SynLED Parallel Photoreactor; selenenylation; electrophile; selenium



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1. Introduction

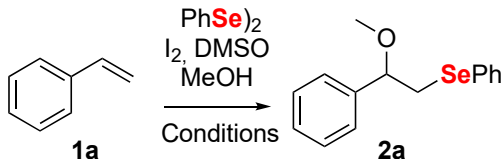
In consideration of several recently reported biological activities, organo-selenium compounds are increasingly attracting the interest of the scientific community. These activities were reported not only as redox modulators but also as selective enzymatic inhibitors, opening up their possible use as antimicrobial, antiviral, and anticancer agents [1–8]. Organo-selenium derivatives are interesting intermediates in organic synthesis due to some peculiar aspects of the selenium reactivity [9–11]. For these reasons, their preparation using modern technologies is an attractive and challenging field of research.

Organo-selenium functionalities can be easily introduced in an organic substrate using electrophilic, nucleophilic, or radical selenium species [12]. Among these protocols, the electrophilic protocols, easily generable by the oxidation of a Se-Se bond, are likely the most studied and applied in a plethora of different synthetic transformations [13]. In order to avoid undesired side reactions, several methods were developed to prepare new, selenium-centered electrophiles that have a scarcely nucleophilic anion [14]. Recently, the catalytic use of I₂ in the presence of a stoichiometric amount of oxidant (DMSO or H₂O₂) was demonstrated to be particularly efficient and ecofriendly for many oxidative transformations, including the oxidative Se-Se bond cleavage [15,16]. In this latter case, the reaction is normally slow but can be efficiently accelerated by using conventional heating or microwave irradiation. In the present work, we report the first results obtained using BlueLed light as an alternative source of activation. In particular, we used the commercially available SynLED photoreactor, which allows for the parallel screening of up to 16 simultaneous reactions.

2. Results and Discussion

The reaction conditions were preliminarily optimized using the selenomethoxylation of styrene (**1a**) as a model reaction. Results were obtained using different amounts of diselenide, iodine, DMSO, and MeOH, as well as by comparing the different activating conditions summarized in Table 1. The positive role of the BlueLED irradiation is clearly evidenced by the comparison of the results reported in entries 1, 2, and 3. In this latter case, an appreciable conversion (63%) was obtained in a very short reaction time with respect to those necessary to convert **1a** into **2a** at room temperature (76% in 24 h) or at 50 °C (80% in 10 h). An excess of diselenide (entry 6) and starting material **1a** (entry 8) produced a positive effect in the overall conversion calculated by NMR (considering, in each case, the stoichiometrically limiting reagent). For a deeper investigation, all reactions were monitored for six hours and the results, reported in Figure 1, showed that a quantitative conversion can be obtained in 4 hours by using an excess of the substrate, demonstrating that these conditions are superior to all others tested.

Table 1. Preliminary screening of the reaction conditions.

						
Entry	PhSe) ₂	I ₂	DMSO	MeOH	Conditions	Yield%
1	1 equivalent	20 mol%	1 equivalent	2 equivalent	Heating 50 °C, 10 h	80
2	1 equivalent	20 mol%	1 equivalent	2 equivalent	rt, 24 h	76
3	1 equivalent	20 mol%	1 equivalent	2 equivalent	BlueLED, 3 h	63
4	1 equivalent	20 mol%	3 equivalent	2 equivalent	BlueLED, 3 h	55
5	1 equivalent	20 mol%	1 equivalent	10 equivalent	BlueLED, 3 h	57
6	2 equivalent	20 mol%	1 equivalent	2 equivalent	BlueLED, 3 h	76
7	1 equivalent	10 mol%	1 equivalent	2 equivalent	BlueLED, 3 h	50
8	0.25 equivalent	20 mol%	0.5 equivalent	1 equivalent	BlueLED, 3 h	85

¹ Calculated by NMR, based on considering the limiting reagent.

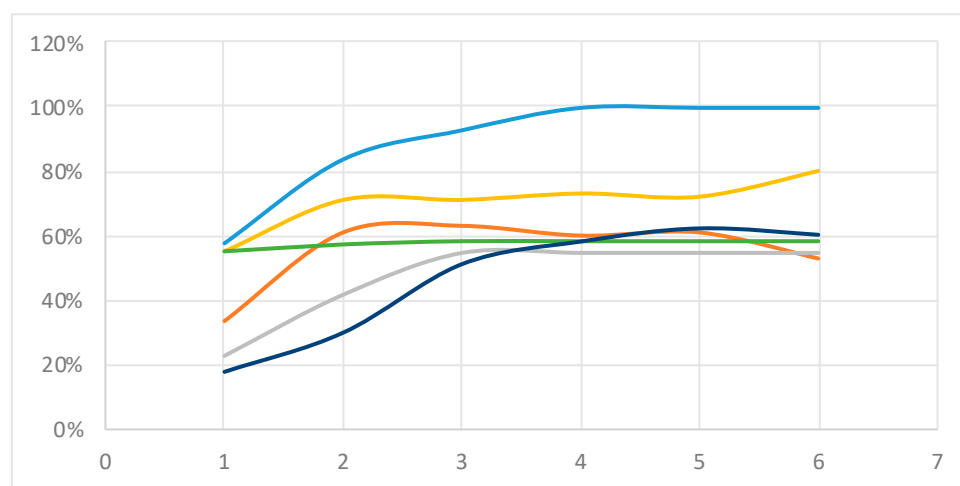


Figure 1. Evaluation of the conversion, calculated by ¹H-NMR, of the crude in the first six hours of reaction, using the conditions depicted in Table 1, Entry 8 (light blue); Entry 6 (yellow); Entry 3 (orange); Entry 5 (green); Entry 4 (grey); and Entry 7 (dark blue).

With the best conditions in hand, we performed a brief scope investigation using different alcohols and different substrates. These results are summarized in Figures 2 and 3, respectively.

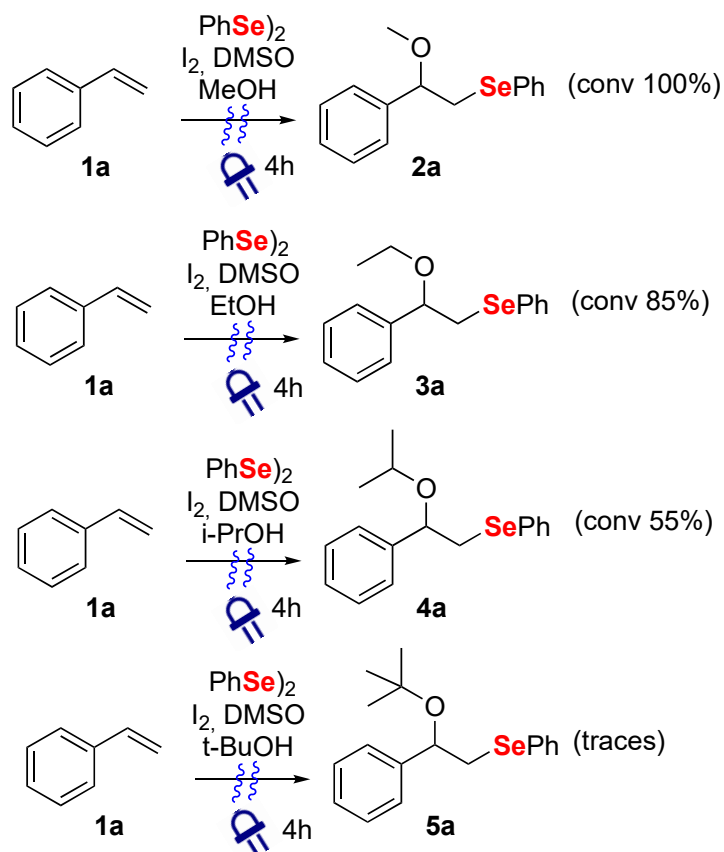


Figure 2. Scope of the alcohols.

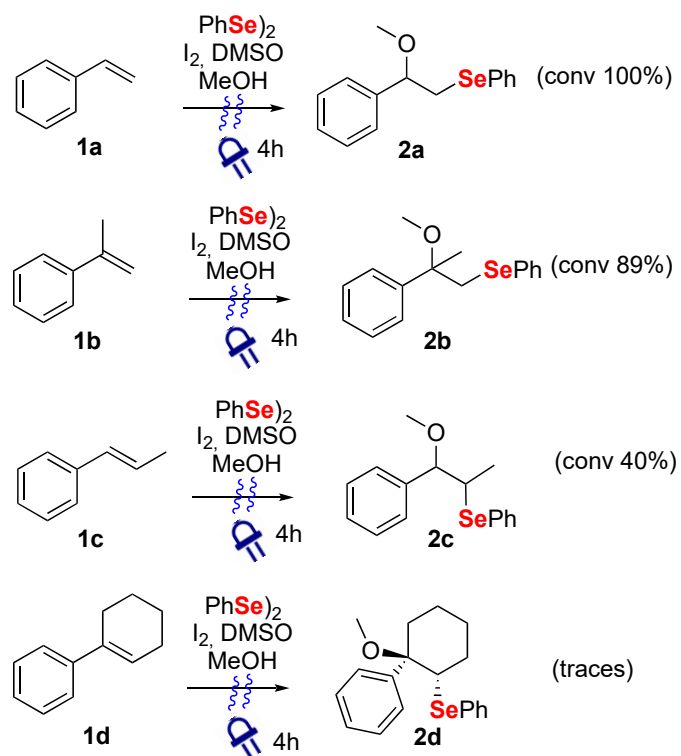


Figure 3. Scope of the substrates.

The reactivity of different alcohols reflects the relative steric demands, affording the selenide **2a** and **3a** in excellent yields and **4a** in a 55% yield, while only traces of **5a** were observed in the case of *t*-BuOH.

Similarly, it was noted that when the substrates **1a–1c** were subjected to the conditions optimized for the methoxyselenenylation, they afforded **2a**, **2b**, and **2c** in 100%, 89%, and 40% yields, respectively. The most sterically constrained selenide, **2d**, was only identified in traces.

Interestingly, the reaction from **1c** afforded the formation of one of the two possible stereoisomers (**2c**) arising from a stereospecific *trans* addition to the double bond. This demonstrates that the reaction mechanism involved the intermediate formation of a seleniranium ion, which can be formed only considering the involvement of an electrophilic selenium species.

A mechanism can be speculated based on these considerations, as is reported in Figure 4. The Blue LED irradiation activates the Se–Se bond, leading to the intermediate formation of a radical that readily reacts with iodine, affording the electrophilic selenenyl iodide (PhSe–I), which is responsible for the selenenylation reaction by following a classical mechanism via a seleniranium-ion intermediate.

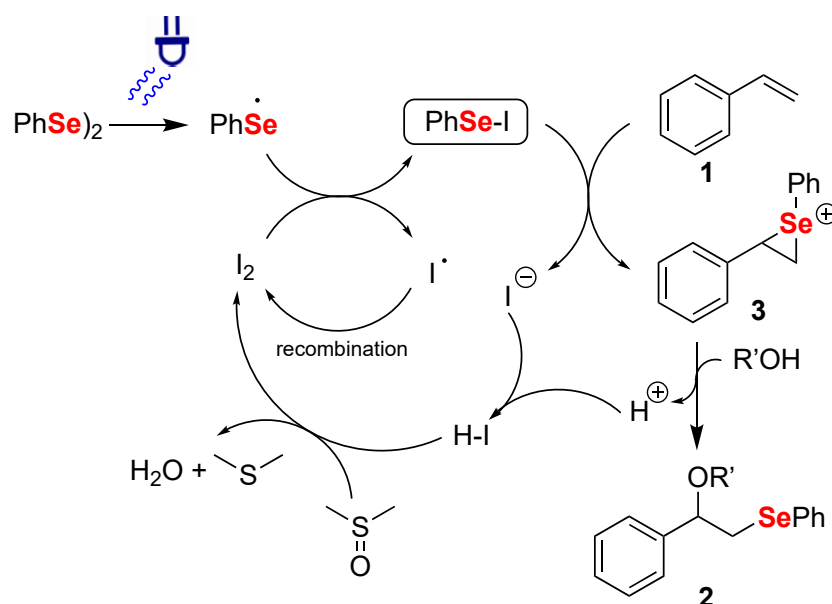


Figure 4. Proposed reaction mechanism.

Iodine is regenerated by the recombination of the corresponding radicals or by the oxidation of the iodide, promoted by the DMSO. The rate-limiting step of the reaction is likely the formation of the seleniranium ion; for this reason, an excess of substrate produced an increase in the conversion yield.

3. Conclusions

In conclusion, we demonstrated that the Se–Se bond oxidation mediated by I_2 /DMSO can also be activated by Blue LED irradiation. The small scope reported in this communication demonstrates an appreciable applicability of the method, suggesting its application in other electrophilic selenenylation reactions.

4. Experimental

The reactions were conducted in closed vials. Unless otherwise noted, solvents and reagents were used as received. Analytical, thin-layer chromatography (TLC) was performed on aluminum foil sheets pre-coated with Merck silica gel 60 F254, visualized by UV irradiation or by iodine staining. Sigma Aldrich silica gel (230–400 mesh) was used for

flash chromatography, and the silica gel Kieselgel 60 (70–230 mesh) was used for column chromatography. NMR experiments were obtained at 25 °C on a Bruker DRX 400 spectrometer operating at 400 MHz for ^1H and 100.62 MHz for ^{13}C . ^1H and ^{13}C chemical shifts (δ) were reported in parts per million (ppm), and they were relative to the TMS 0.0 ppm and the residual solvent peak of CDCl_3 at δ 7.26 and δ 77.00 in ^1H and ^{13}C NMR, respectively. Data are reported as follows: chemical shift (multiplicity; number of hydrogens; coupling constants, where applicable; and assignment, where possible). Abbreviations are as follows: s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublet), dt (double of triplet), tt (triplet of triplet), m (multiplet), and br s (broad signal). The coupling constant (J) is quoted in Hertz (Hz) to the nearest 0.1 Hz. GC-MS analyses were carried out with an HP-6890 gas chromatograph (dimethyl silicone column, 12.5 m) equipped with an HP-5973 mass selective detector (Hewlett-Packard, Waldbronn, Germany).

All the reaction were performed using a SynLed parallel Photoreactor (Merck KGaA, Darmstadt, Germany) operating in a 465–470 nm spectral range.

4.1. General Optimized Procedure

Styrene (0.5 mmol; 57 μL) was added to $(\text{PhSe})_2$ (0.125 mmol; 39 mg), I_2 (0.012 mmol; 3.2 mg), and the appropriate alcohol (0.5 mmol) in closed vial. The reaction mixture was stirred for the time indicated in Table 1 and Graph 1 at room temperature (25 °C) under BlueLED irradiation. The reactions were monitored by TLC and NMR. The reaction mixture was quenched with water, extracted with EtOAc ($\times 3$), dried with Na_2SO_4 anhydrous, and then concentrated under reduced pressure.

4.2. Spectral Data of Selected Compounds

(2-Methoxy-2-phenylethyl)-phenyl-selane (**2a**) Yellow oil, ^1H -NMR (400 MHz, CDCl_3): δ = 7.54–7.48 (m, 2H), 7.38–7.24 (m, 8H), 4.37 (dd, J = 5.0 Hz; J = 9.0 Hz, 1H), 3.36 (dd, J = 9.0 Hz; J = 13.0 Hz, 1H), 3.27 (s, 3H), 3.13 (dd, J = 5.0 Hz; J = 13.0 Hz, 1H) ppm. ^{13}C -NMR (100 MHz, CDCl_3): δ = 140.9; 132.6; 130.7; 129.1; 128.6; 128.1; 126.8; 126.7; 83.2; 57.1; 35.4 ppm. GC-MS (70 eV; EI): m/z (relative intensity) = 292 (18) $[\text{M}]^+$; 157 (6); 121 (100); 91 (16); 77 (17).

(2-Ethoxy-2-phenylethyl)-phenyl-selane (**2b**) ^1H -NMR (400 MHz, CDCl_3): δ = 7.46–7.44 (m, 2H), 7.30–7.18 (m, 8H), 4.43 (m, 1H), 3.37–3.28 (m, 3H), 3.07 (m, 1H), 1.15 (t, J = 9.48 Hz, 3H) ppm. ^{13}C -NMR (100 MHz, CDCl_3): δ = 141.6; 132.5; 130.9; 129.0; 128.5; 127.9; 126.7; 126.6; 81.4; 64.7; 35.6; 15.2 ppm. GC-MS (70 eV; EI): m/z (relative intensity) = 306 (13) $[\text{M}]^+$; 157 (16); 135 (100); 107 (46); 77 (27).

(2-Isopropoxy-2-phenylethyl)-phenyl-selane (**2c**) ^1H -NMR (400 MHz, CDCl_3): δ = 7.55–7.51 (m, 2H), 7.50–7.25 (m, 8H), 4.60 (m, 1H), 3.55 (m, 1H), 3.35 (dd, J = 8.6 Hz; J = 12.0 Hz, 1H), 3.12 (dd, J = 4.8 Hz; J = 12.0 Hz, 1H), 1.21 (d, J = 6.0 Hz, 3H), 1.13 (d, J = 6.2 Hz, 3H) ppm. ^{13}C -NMR (100 MHz, CDCl_3): δ = 142.4; 132.2; 131.0; 128.9; 128.4; 127.7; 126.5; 78.7; 69.7; 36.0; 23.3; 21.3 ppm. GC-MS (70 eV; EI): m/z (relative intensity) = 320 (9) $[\text{M}]^+$; 158 (19); 149 (53); 107 (100); 77 (25).

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