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I_2 Catalyzed DMSO Oxidation of Se-Se Bond Activated by the Use of SynLED Parallel Photoreactor ® †

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Abstract: Among different green oxidative protocols, I_2 catalyzed DMSO systems have recently received considerable attention being greener, efficient, atom-economical, low-cost and offering the possibility to perform reactions under safe and mild conditions. Particularly interesting is the application in the chalcogen-chalcogen bond activation that allows the in-situ formation of electrophilic species promoting a number of Se-C bond formation. In these reactions iodine acts as a catalytic oxidant continuously regenerated by the DMSO that can be used in stoichiometric amount under solvent free conditions. Methoxyselenylation reactions can be performed at room temperature but the reaction takes over 24 h to reach appreciable conversion yields. In this paper the 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

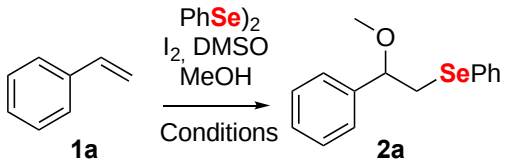
Organoselenium compounds are even more attracting the interest of the scientific community in consideration of several biological activities that were recently reported not only as redox modulators but also as selective enzymatic inhibitors, opening their possible use as antimicrobial, antiviral and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

Organoselenium functionalities can be easily introduced in an organic substrate using electrophilic, nucleophilic or radical selenium species [12]. Among these protocols the electrophilic ones, easily generable by the oxidation of a Se-Se bond are probably 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 having a scarcely nucleophilic anion [14]. Recently the catalytic use of I_2 in the presence of a stoichiometric amount of oxidant (DMSO or H_2O_2) was demonstrated to be particularly efficient and ecofriendly in a lot of 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 the use of conventional heating or microwave irradiation. In the present work we report the first results obtained using BlueLed light as alternative source of activation. In particular we used the commercially available SynLED photoreactor that allows the parallel screening up to 16 simultaneous reactions.

2. Results and Discussion

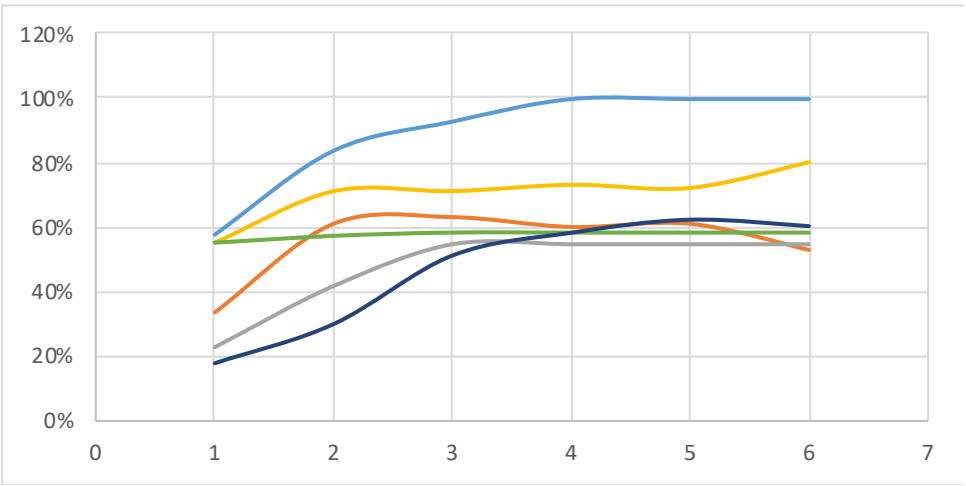
The reaction conditions were preliminary optimized using the selenomethoxylation of styrene (1a) as a model reaction. The results obtained using different amounts of diselenide, iodine, DMSO and MeOH, as well as comparing different activating conditions are summarized in Table 1. The positive role of 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 respect 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) as well as of 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 the reactions were monitored for six hours and the results, reported in graph 1, showed that using an excess of the substrate a quantitative conversion can be obtained in 4 h demonstrating that these conditions are superior to all the other tested.

Table 1. Preliminary screening of the reaction conditions.



Entry	PhSe)$_2$	I$_2$	DMSO	MeOH	Conditions	Yield%
1	1 equiv	20 mol%	1 equiv	2 equiv	Heating 50 °C, 10 h	80
2	1 equiv	20 mol%	1 equiv	2 equiv	rt, 24 h	76
3	1 equiv	20 mol%	1 equiv	2 equiv	BlueLED, 3 h	63
4	1 equiv	20 mol%	3 equiv	2 equiv	BlueLED, 3 h	55
5	1 equiv	20 mol%	1 equiv	10 equiv	BlueLED, 3 h	57
6	2 equiv	20 mol%	1 equiv	2 equiv	BlueLED, 3 h	76
7	1 equiv	10 mol%	1 equiv	2 equiv	BlueLED, 3 h	50
8	0.25 equiv	20 mol%	0.5 equiv	1 equiv	BlueLED, 3 h	85

[1] Calculated by NMR based considering the limiting reagent.



Graph 1. Evaluation of the conversion calculated by ^{1}H-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); entry 7 (dark blue).

With the best conditions in hands, we performed a brief scope investigation using different alcohols and different substrates. All these results are here summarized in Figure 1 and Figure 2, respectively.

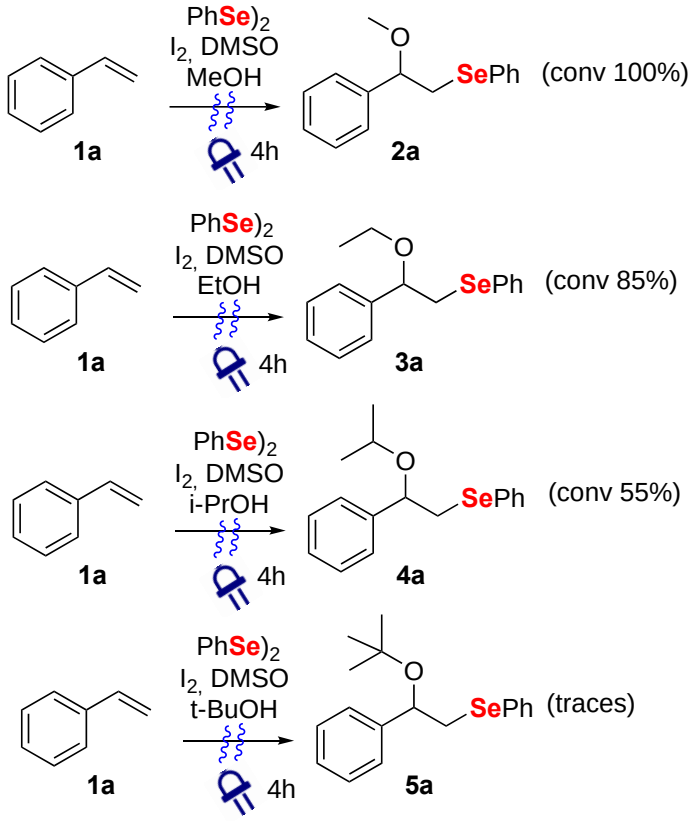


Figure 1. Scope of the alcohols.

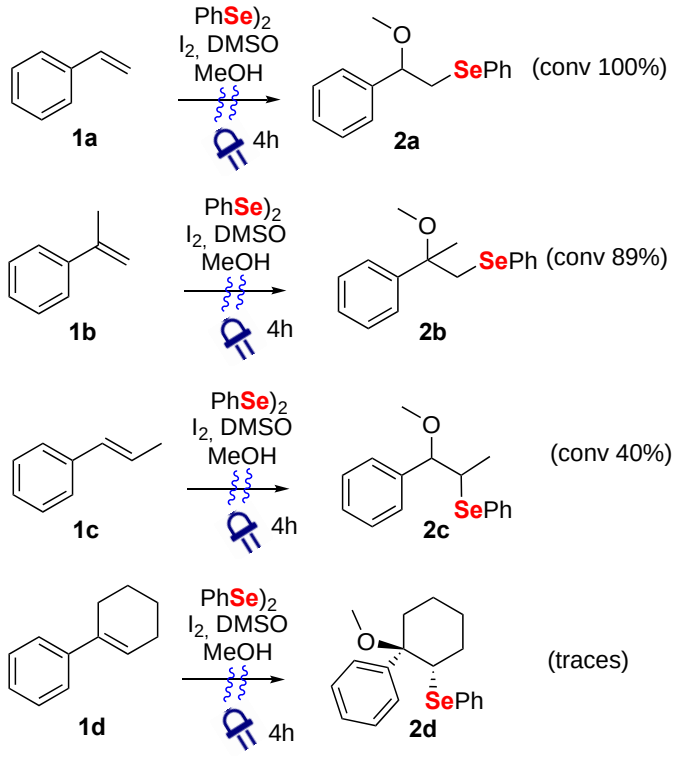


Figure 2. Scope of the substrates.

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

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% yield, respectively and the most sterically constrained selenide **2d** only 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 involves the intermediate formation of a seleniranium ion that can be formed only considering the involvement of an electrophilic selenium specie.

Based on these considerations a mechanism can be speculated as reported in Figure 3. The Blue LED irradiation activates the Se-Se bond leading the intermediate formation of a radical cation that readily reacts with iodine affording the electrophilic mixture (PhSe-I + $PhSe^+$) that is responsible of the selenenylation reaction, following a classical mechanism via seleniranium ion intermediate.

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

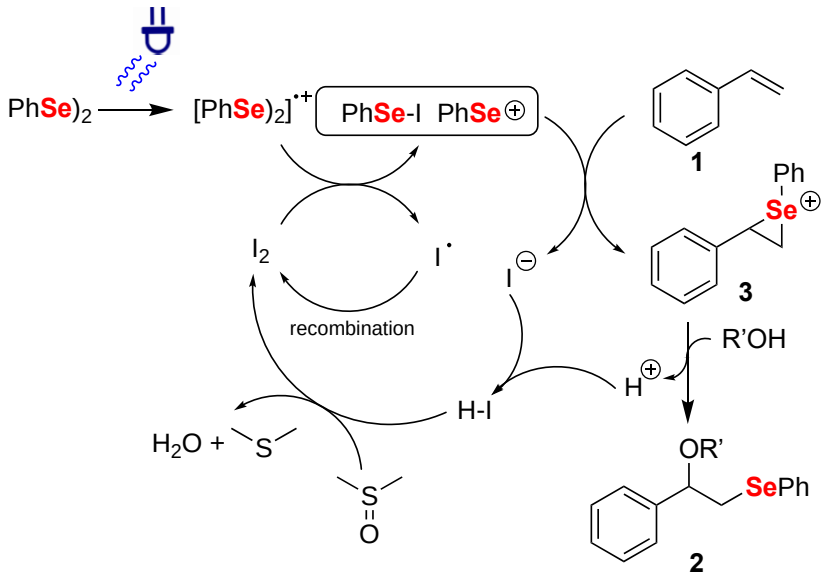


Figure 3. Proposed reaction mechanism.

3. Conclusion

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

4. Experimental

Reactions were conducted in closed vials. Solvents and reagents were used as received unless otherwise noted. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254 precoated aluminum foil sheets and visualized by UV irradiation or by iodine staining. Sigma Aldrich silica gel (230-400 mesh) was used for flash chromatography and 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 ^{1}H and 100.62 MHz for ^{13}C. ^{1}H and ^{13}C chemical shifts (δ) are reported in parts per million (ppm) and they are relative to TMS 0.0 ppm and the residual solvent peak of $CDCl_3$ at δ 7.26 and δ 77.00 in ^{1}H 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), br s (broad signal). Coupling constant (J) quoted in Hertz (Hz) to the nearest 0.1 Hz. GC-MS analyses were carried out with an HP-6890 gas chromatography (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 Phtoreactor (Merck KGaA, Darmstadt, Germany) operating in 465-470 nm spectral range.

4.1. General Optimized Procedure

Styrene (0.5 mmol, 57 μL) was added with $(PhSe)_2$ (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 a water, extracted with EtOAc (× 3), dried with Na2SO4 anhydrous and then concentrated under reduced pression.

4.2. Spectral Data of Selected Compounds

(2-Methoxy-2-phenylethyl)-phenyl-selane (**2a**) Yellow oil, ^{1}H-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) [M]+; 157 (6); 121 (100); 91 (16); 77 (17).

(2-Ethoxy-2-phenylethyl)-phenyl-selane (**2b**) ^{1}H-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) [M]+; 157 (16); 135 (100); 107 (46); 77 (27).

(2-Isopropoxy-2-phenylethyl)-phenyl-selane (**2c**) ^{1}H-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. 13C-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) [M]+; 158 (19); 149 (53); 107 (100); 77 (25).

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