Eco-friendly catalytic aminoselenation of alkenes: a green alternative for obtaining potentially active compounds

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† Presented at the 1st International Electronic Conference on Catalysis Sciences, 10–30 November 2020; Available online: https://sciforum.net/conference/ECCS2020

Published: 10 November 2020

Abstract: In this work, a new ecological approach to the selenofunctionalization of alkenes has been described. Using I₂ as catalyst, DMSO as oxidant, under microwave irradiation (MW) in a solvent- and metal-free method. The general idea is to combine organoselenium compounds and triazole nuclei to obtain molecules capable of becoming a powerful class due to their potential pharmacological activity. However, most methods that involve the functionalization of alkenes are generally mediated by the use of transition metals or reagents in large stoichiometric quantities. Thus, the development of direct, clean and environmentally appropriate procedures, which are in accordance with the principles of Green Chemistry, for the synthesis of these compounds remains highly desirable. Thus, the present work developed the synthesis of β-amino selenides with only 20 minutes of reaction time, following the conditions previously mentioned. In addition, encouraged by these results, the scope of the reaction was expanded using also diorganosil disulfides and ditellurides, obtaining molecules with good to excellent yields. Finally, compared to traditional methods, our methodology is a lightweight, metal-free, simple and practical tool for selenofunctionalization of alkenes and is considered a promising alternative in the development of new drugs with potential biological activities.

Keywords: selenium; aminoselenation; green chemistry

1. Introduction

The chemistry of organoselenium compounds has many similarities to the chemistry of organosulfur. However, due to the greater polarization of its electrons, C-Se bonds are weaker and due to the selenium’s capacity for hypervalence, the transformations of compounds and reagents of this element generally occur more easily and in milder conditions than those of its family of chalcogen.¹

Selenium-derived molecules play an important role in organic synthesis, biochemistry, medicinal chemistry and materials science.² In particular, organic diselenides, such as diphenyl diselenide have unique properties and can be used as nucleophiles, electrophiles, ligands and also as catalysts in organic reactions.³ These substances also act as therapeutics, which vary from anti-viral and anti-cancer agents,⁴ in addition to presenting a series of antioxidant properties.⁵
On the other hand, nitrogen-containing compounds are present in the active principle of several commercial drugs, and the development of research related to the synthesis and biological study of these substances is of great interest. Especially, in the medicinal field, azoles can easily interact with various enzymes and receptors in organisms through non-covalent interactions, exhibiting broad biological activities such as antibacterial, antifungal, antiviral, anticoagulant, anti-inflammatory, anticancer and antioxidant properties, etc.

Some structures, already reported (Figure 1), resulting from the combination of these two classes of compounds show the potentialization of several desired biological activities. Therefore, the selenofunctionalization of heterocycles containing nitrogen can be considered a promising alternative in the development of new drugs.

![Figure 1](image_url)

**Figure 1.** Selected pharmacologically active selenium-containing heterocycles.

The construction of these versatile structures has attracted considerable research attention and, therefore, numerous synthetic methodologies have been developed to introduce selenium atoms into organic compounds. Still, all of these methods have some particular disadvantages, such as long reaction times and the use of large amounts of metals and/or solvents. Therefore, the development of a new environmentally friendly approach to the selenofunctionalization of alkenes remains an important challenge in organic synthesis.

In contrast, the use of microwave irradiation (MW) in organic transformations, including the formation of C-Se and C-S bonds, can provide higher yields in a faster reaction. In addition, with the development of technologies, solvent-free conditions have emerged as a green alternative to organic synthesis and are capable of preventing problems related to flammability and toxicity, as well as significantly reducing the amount of waste generated. In this context, the molecular iodine (I²) emerged as a convenient catalyst in several organic transformations, as it is a non-toxic, non-metallic and low-cost reagent. Thus, the combination of a solvent- and metal-free method with microwave irradiation heating was successfully used for the synthesis of new organocalcogenic compounds.

2. Results and Discussion

We initially chose styrene (1a), diphenyl diselenide (2a) and 1H-benzotriazole (3a) as model substrates to optimize the amidoselenation conditions.
Table 1. Optimization of the reaction conditions\(^{[a]}\).

| # | DMSO (eq) | I\(_2\) (mol%) | T (°C) | Time (min) | Yield\(^{[b]}\) (%) |
|---|----------|-----------------|-------|------------|------------------|
| 1 | 1        | 20              | 50    | 20         | 24               |
| 2 | 1        | 20              | 80    | 20         | 60               |
| 3 | 1        | 20              | 65    | 20         | 73               |
| 4 | 2        | 20              | 65    | 20         | 89               |
| 5 | 2        | 10              | 65    | 20         | 82               |
| 6 | 2        | 15              | 65    | 20         | 76               |
| 7 | 2        | 25              | 65    | 20         | 46               |
| 8 | 3        | 20              | 65    | 20         | 84               |

\(^{[a]}\) Reactions were performed with 1a (2 equivalents), 2a (0.25 mmol) and 3a (2 equivalents) under different concentrations of molecular iodine, DMSO and temperature for 20 minutes. \(^{[b]}\) Yield of the isolated product.

When the reaction was carried out at 50 °C, 1 equivalent of DMSO and 20 molar% of I\(_2\), only 24\% of the target product was obtained (Table 1, entry 1). Under the same conditions, when the temperature was raised to 80 °C, a yield of 60\% was observed (Table 1, entry 2). As the temperature increase was able to directly affect the reaction yield, it was decided to carry it out, also at 65 °C, obtaining a considerable 73\% of the desired product (Table 1, entry 3). Subsequent experiments revealed that the yield of 4a can be increased considerably to 89\% when the reaction was carried out at 65 °C, but using 2 equivalents of DMSO (Table 1, entry 4). Notably, this reaction also worked well with the I\(_2\) percentage drop to 10\%, although even less than the previous entry (Table 1, entry 5). After screening I\(_2\), it was observed that 20 mol\% of it was still the best reaction condition to be tested (Table 1, entries 6 and 7). An increase in the amount of DMSO for three equivalents produced 4a, also with a satisfactory yield of 84\% (Table 1, entry 8). Thus, after widely optimizing the reaction conditions, we established a highly efficient route for the aminoselenation of styrene 1a (Table 1, entry 4).

Using the optimized conditions, we explore the scope of aminoselenation reaction of alkenes testing various diselenides with the results summarized in Table 2. In general, the diselenides containing electron withdrawing or donor groups in the aryl rings readily participated in the reactions, providing the desired α-amino-selenides with good to excellent yields (4b-4g). In addition, 1,2-bis (4-thiophen-2-yl)phenyl diselane with a thiophene ring can also give the desired product 4h in an excellent 82\% yield. In contrast, 1,2-di (naphthalen-2-yl) diselane provided the desired product 4i in 27\% yield.
Inspired by these results, with the reaction conditions optimized at hand, we started to explore the scope of the substrate of this aminoselenation. Thus, some alkenes (5d-f) were examined with 2a and 3a under standard conditions (Table 3).

| Table 3. Substrate scope of alkenes. |
|-------------------------------------|

First, the substituted alkenes 1a and 1b provided products 5a and 5b with yields of 74% and 54%, respectively. While aliphatic alkenes, 1c and 1d supplied products 5c and 5d with yields 40% and 48%, respectively. We also observed that the reaction was considerably affected by the steric effects, since the products of the alkenes 1e and 1f did not form.

The scope of the reaction in relation to the preparation of β-amino selenides was further explored with other chalcogens using a series of diphenyl disulfides and diteluterides as a substrate (Table 4).
Table 4. Substrate scope of diorganoyl dichalcogenides.

The use of diorganoyl disulfides containing donor and electron withdrawer groups provided the desired products (6b-g) with good to moderate yields. The 1,2-di(naphthalen-2-yl) disulfane provided the desired product 6h with a reasonable yield of 42%. While the aliphatic disulfide, 1,2-dicyclohexyl disulfane, provided compound 6i in 20% yield. Regarding the tested ditelurides, diphenyl provided the product 6j with 34% yield. The use of ditelurides containing a withdrawing group (2k) and another donor (2l) of electrons provided their respective products, 6k and 6l, with lower yields of 19% and 16%, indicating that the presence of substituents in the ring considerably affects the reaction.

3. Conclusion

In short, a fast, economical and solvent and metal-free methodology was developed, with sustainable and highly efficient reaction conditions. In addition, due to its broad scope of substrates, it must have great synthetic potential for the construction of several compounds containing selenium and other chalcogens. Finally, the next step in this work will then be to analyze the potential biological activity of these compounds.

References
1. Ward, V. R. Aspects of Organoselenium Chemistry. Doctor of Philosophy, The University of Adelaide: Adelaide, Australia, 2012.
2. Freudendahl, D. M. Green Chemistry with Selenium Reagents: Development of Efficient Catalytic Reactions. Angew. Chem., Int. Ed. 2009, 48, 8409.
3. Freudendahl, D. M.; Shahzad, S. A.; Wirth, T. Recent Advances in Organoselenium Chemistry. Eur. J. Org. Chem. 2009, 2009, 1649.
4. Shao, L. Recent progress in selenium-catalyzed organic reactions. Org. Chem. Front. 2019, 6, 2999.
5. Li, H.; Liao, L.; Zhao, X. Organoselenium-Catalyzed Aza-Wacker Reactions: Efficient Access to Isoquinolinium Imides and an Isoquinoline N-Oxide. Synlett 2019, 30, 1688.
6. Casas, J. S. Diorganotin(IV) complexes of pyridoxal thiosemicarbazone: synthesis, spectroscopic properties and biological activity. J. Inorg. Biochem. 1998, 69, 283–292.
7. Teitz, Y. Inhibition of human immunodeficiency virus by N-methylisatin-beta 4':4'-diethyldihydrosemicarbazone and N-allylisatin-beta-4':4'-diallydihydrosemicarbazone. Antiviral res. 1994, 24, 305–314.
8. Mugesh, G.; Du Mont, W.W.; Sies, H. Chemistry of biologically important synthetic organoselenium compounds. *Chem. Rev.* 2001, 101, 2125–2179.
9. Hili, R.; Yudin, A.K. Making carbon-nitrogen bonds in biological and chemical synthesis. *Nat. Chem. Biol.* 2006, 2, 284.
10. Ricci, A. *Amino Group Chemistry: From Synthesis to the Life Sciences*, 1st ed.; Wiley-CVH, Weinheim, Germany, 2007.
11. Zhang, H.; Gan, L.; Wang, H.; Zho, C. New Progress in Azole Compounds as Antimicrobial Agents. *Mini-Reviews in Med. Chem.* 2017, 17, 122–166.
12. Desai, D. Synthesis and evaluation of the anti-inflammatory properties of selenium-derivatives of celecoxib. *Chem. Biol. Interact.* 2010, 188, 446–456.
13. Kumar, S. Facile synthesis, structural evaluation, antimicrobial activity and synergistic effects of novel imidazo[1,2-a]pyridine based organoselenium compounds. *Eur. J. Med. Chem.* 2016, 123, 916.
14. Wen, Z. 3-(3,4,5-Trimethoxyphenylselenyl)-1H-indoles and their selenoxides as combretastatin A-4 analogs: Microwave-assisted synthesis and biological evaluation. *Eur. J. Med. Chem.* 2015, 90, 184–194.
15. Vieira, B. M. Ultrasound-Assisted Synthesis and Antioxidant Activity of 3-Selanyl-1 H-indole and 3-Selanylimidazo[1,2-a]pyridine Derivatives. *J. Asian, Org. Chem.* 2017, 6, 1635–1646.