SHORT COMMUNICATION

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Synthesis of 3-Selenylindoles under Ecofriendly Conditions

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The preparation of biologically relevant 3-selenylindoles by a greener protocol by using a catalytic amount of K_2CO_3 and ethanol as a biosolvent in a system open to air was explored. Through this easy approach, 3-selenylindoles with different functionalities were obtained in good yields by a radical pathway.

Introduction

The indole core is one of the most fascinating heterocycles found in nature.[1] It is present in many important biological structures, such as the amino acid tryptophan, the neurotransmitter serotonin, and drugs used in several types of treatments.[2] Owing to their biological and pharmaceutical properties, chalcogenylindoles have attracted interest from both industry and academia.

This class of compounds has been shown to have therapeutic value in the treatment of different diseases including cancer,[3] HIV,[4] allergies,[5] and heart-related disorders.[6] Also, recent studies have shown that 3-arylthioindoles are potent inhibitors of tubulin polymerization, which is a proven strategy to combat the growth of tumor cells.[7] For instance, compound **A** (Figure 1) is able to interfere with the tubulin system by acting as a powerful inhibitor of its polymerization even at low concentrations.[8] Analogously, compound **B** shows potent antiviral activity against smallpox.[9]

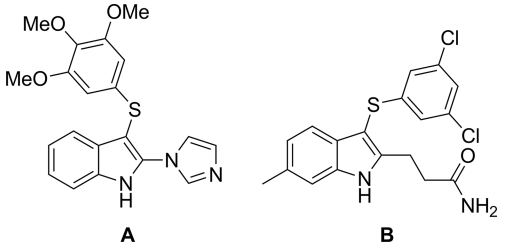

Figure 1. Some bioactive 3-arylthioindoles.

Similarly, the activity of organoselenium compounds has been exploited in different areas of chemistry such as biochemistry and materials.[10] In addition, these compounds exhibit fascinating biological profiles, notably their ability to mimic the enzyme glutathione peroxidase, which plays a crucial role in the detoxification of reactive oxygen species in mammalian cells.[11]

Because of the importance of organochalcogen compounds in many bioactive products and because of the wide spectrum of biologically active indoles, some synthetic methods for the construction of 3-chalcogenylindoles have been reported. These compounds can be prepared through electrophilic cyclization of *o*-alkynylanilines by using electrophilic species such as organochalcogen agents mediated by a transition metals[12] or performed in the presence of iodine reagents.[13] Another process for obtaining this class of compounds involves the direct chalcogenylation of the indole moiety through the use of different agents such as *N*-chalcogenoimides,[14] quinone mono-O,S-acetals,[15] sulfonylhydrazides,[16] dichalcogenides,[17] and sulfonium salts.[18] On the other hand, the development of environmentally friendly methods has attracted significant attention in recent years.[7a,19] The aim of this approach is to minimize environmental impacts, particularly those caused by the use of toxic solvents and transition metals. In this regard, the use of green solvents is highly desirable, and several solvents have been used successfully for this purpose, for instance, water, ionic liquids, glycerol, polyethylene glycol (PEG), and dimethyl carbonate among others. In this context, reactions involving the use of ethanol as a solvent in organic synthesis have emerged, and they are employed in several transformations including epoxide ring opening,[20] C–C bond formation,[21] and Biginelli cyclocondensation.[22] Furthermore, ethanol is considered to be a biosolvent, as it is produced from renewable sources.[23] In addition, ethanol is easy to handle and is associated with low cost and low environmental and health risks.

Our research group has focused on the development of more sustainable methods for the preparation of organoselenium compounds. Recently, we reported the synthesis of 3-chalcogenylindoles by using indoles and diorganyl dichalcogenides as starting materials catalyzed by I_2 under microwave irradiation.[24]

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In 2013, Zhang and co-workers[25] reported the synthesis of 3-sulfenylindoles by using K_2CO_3 (0.5 equiv.) and DMSO as the solvent with an excess amount of disulfides. After a reaction time of 9 h, they obtained a series of 3-sufenylindoles in good yields. Inspired by the development of new environmentally friendly methodologies involving the preparation of biologically relevant organoselenium compounds and considering that the indole nucleus is of biological interest, we decided to explore the synthesis of 3-selenylindoles. Despite the success of the synthesis of this class of compounds reported by our group, we considered the possibility of developing a simple, rapid, and environmentally adequate method, in which the use of microwave equipment could be avoided. In this context, we developed an alternative and greener protocol for the synthesis of these compounds by treating indoles with diaryl diselenides promoted by a catalytic amount of K_2CO_3 and with the use of ethanol as a green solvent in a short reaction time.

Results and Discussion

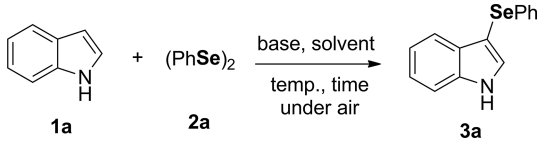
In an attempt to determine the optimal reaction conditions, in our initial study we started from the optimization of the reaction of 1*H*-indole (**1a**) with diphenyl diselenide (**2a**) in the presence of a base in an open-to-air system (Table 1). Initially, the influence of the reaction medium was evaluated by using different ionic liquids owing to the properties of these materials, such as their low toxicity, good stability, and catalytic ability. First, the ionic liquid 1-butyl-3-methylimidazolium hexafluorophosphate ([bmim]-PF_6) was used, and the product was obtained in 83% yield (Table 1, entry 1). However, if we used [bmim]Br the yield decreased to 75%, which indicated that the counterion influences the formation of product **3a** (Table 1, entry 2).

Notably, if the reaction was performed in the presence of the polymer PEG-400 for 14 h, a significant increase in the yield was observed (99%). This level of yield was maintained even if the solvent was recycled once, as the desired product was delivered in 98% yield (Table 1, entry 4). This demonstrated that PEG-400 has the potential for use in this type of transformation. This reaction was also conducted over 2 h; however, this led to a decrease in the yield (71%; Table 1, entry 5). We also tested glycerol as a sustainable solvent, but in this case the desired product was obtained in only 47% yield (Table 1, entry 6).

In view of the interest in the use of a low-costing solvent obtained from a renewable source, ethanol was considered as an alternative. Upon conducting the reaction with ethanol overnight at 40 °C, the corresponding product was obtained in 95% yield (Table 1, entry 3). This result encouraged us to continue exploring the reaction in ethanol medium. The reaction was then performed at room temperature for 24 h, which gave product **3a** in 99% yield (Table 1, entry 9). Upon increasing the temperature to 60 °C for 3.5 h, it was observed that the yield remained at a quantitative level (99%; Table 1, entry 10).

The reaction was also conducted in the absence of solvent, but the desired product was obtained in only 25% yield (Table 1, entry 7). We also investigated the influence of ultrasonic irradiation on this reaction by using PEG-400 (Table 1, entry 8) and ethanol (Table 1, entry 11) as solvents, but the results were not satisfactory, as the product was obtained in yields of 61 and 75%, respectively. Finally, we tested a mixture of ethanol and water as the solvent, but the yield decreased considerably (20%; Table 1, entry 12).

Table 1. Optimization of the reaction conditions.[a]



Entry	Base	Solvent	Temp. [°C]	Time [h]	Yield[b] [%]
1	K_2CO_3	[bmim]PF_6	100	14	83
2	K_2CO_3	[bmim]Br	100	14	75
3	K_2CO_3	EtOH	40	14	95
4	K_2CO_3	PEG-400	100	14	99/98[c]
5	K_2CO_3	PEG-400	100	2	71
6	K_2CO_3	glycerol	100	14	47
7	K_2CO_3	–	100	14	25
8	K_2CO_3	PEG-400[d]	25	3	61
9	K_2CO_3	EtOH	25	24	99
10	K_2CO_3	EtOH	60	3.5	99
11	K_2CO_3	EtOH[d]	25	2	75
12	K_2CO_3	EtOH/H_2O	60	2	20
13	K_2CO_3	EtOH	60	1	63
14	K_2CO_3	EtOH	60	2	96
15	K_2CO_3	EtOH	60	3	99
16	K_2CO_3	EtOH	25	2	31
17	K_2CO_3	EtOH	40	2	56
18	K_2CO_3	EtOH	80	2	97
19	–	EtOH	60	2	0
20	KOH	EtOH	60	2	99
21	Na_2CO_3	EtOH	60	2	trace
22	Et_3N	EtOH	60	2	trace
23	Cs_2CO_3	EtOH	60	2	99

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.5 mmol), base (0.25 mmol), solvent (1 mL), at a specific time. [b] Yield of isolated product based on **3a**. [c] Reused PEG-400. [d] The reaction was irradiated in an ultrasonic bath.

At this point, it is important to note that with our method the preparation of 3-selenylindole (**3a**) can be performed by using PEG-400 at 100 °C or ethanol at 60 °C, as both provide the desired product in almost quantitative yield. However, we decided to continue the investigation and improve this reaction by employing ethanol as the solvent, as it is inexpensive, widely available, and obtained from renewable sources.

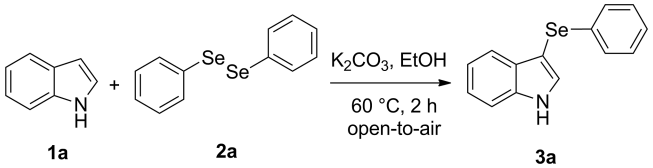
After screening the solvents, we set out to establish the appropriate reaction time for this transformation. Upon performing the reaction over 1 h, product **3a** was obtained in 63% yield (Table 1, entry 13). Upon increasing the reaction time to 2 h the yield increased to 96% (Table 1, entry 14), and after 3 h of reaction the yield was 99% (Table 1, entry 15). Thus, considering a balance of yield versus reaction time, 2 h was selected as providing the most adequate combination.

In the next step, the effect of temperature on the reaction system was evaluated. Upon performing the reaction at room temperature the yield was 31% (Table 1, entry 16), whereas at 40 °C the yield increased to 56% (Table 1, entry 17). If the reaction was performed at 60 °C, the desired product was obtained in 96% yield, whereas at 80 °C the yield was 97% (Table 1, entry 18). On the basis of these results, we established that a reaction temperature of 60 °C was the most suitable.

The effect of an alkaline medium was also investigated. If the reaction was performed in the absence of base, the formation of the desired product was not observed (Table 1, entry 19). This result showed that the presence of a base was essential for this transformation. With the use of a strongly alkaline base, such as KOH, a quantitative yield was observed (Table 1, entry 20). A similar result was obtained if Cs_2CO_3 was employed (Table 1, entry 23). On the other hand, if Na_2CO_3 (Table 1, entry 21) was used, only a trace amount of the desired product was obtained. This result can be rationalized in terms of the difference in the solubilities of the bases K_2CO_3 and Na_2CO_3 in alcohol media, as the former is about 20 times more soluble than the latter.[26] If Et_3N (Table 1, entry 22) was used, product **3a** was obtained in only trace amounts. On the basis of these results, it was established that the most suitable base for this transformation was K_2CO_3, mainly as a result of its availability and low cost.

To promote atom economy, we examined the stoichiometry of the starting materials (Table 2). If the reaction was performed with 50 mol-% of base, product **3a** was obtained in 96% yield (Table 2, entry 1). The same yield was observed upon using 20 mol-% (Table 2, entry 2), which indicated that the reaction occurs in a catalytic way.

Table 2. Study on the stoichiometry of the reactants in the formation of 3-selenylindole (**3a**).



1a 2a 3a

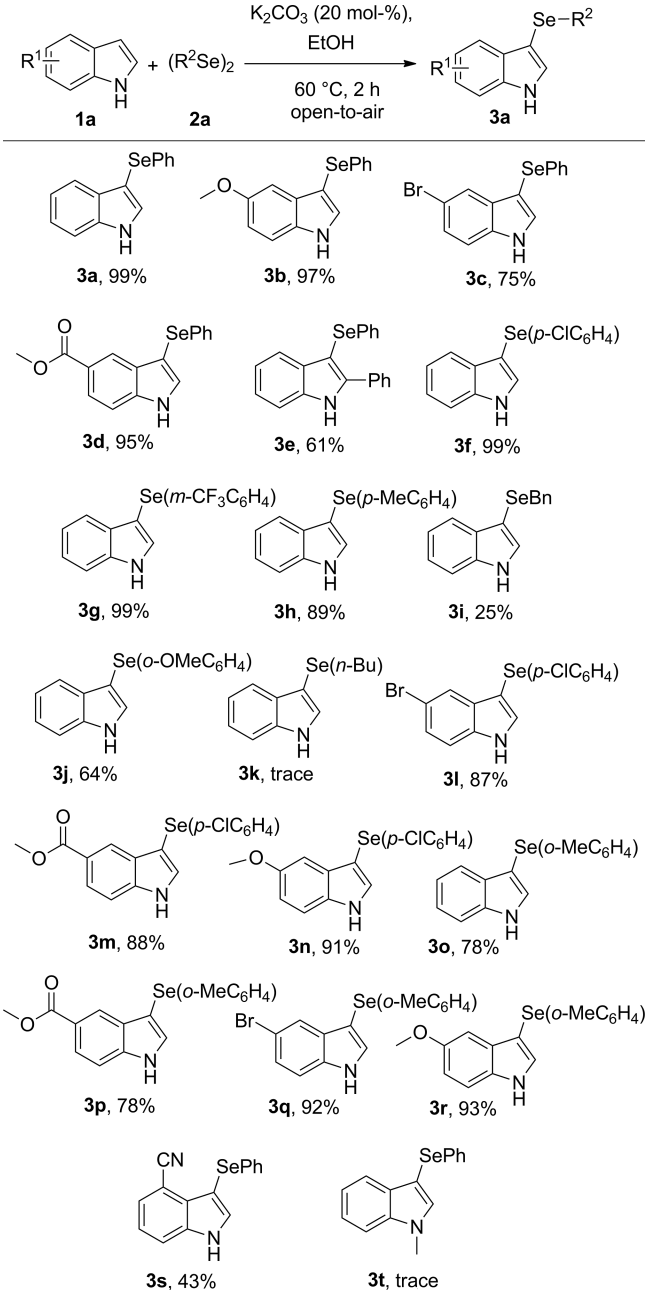
Entry	K_2CO_3 [mol-%]	Diselenide **2a** [equiv.]	Yield[a] [%]
1	50	2	96
2	20	2	96
3	10	2	66
4	20	1.5	99
5	20	1	68

[a] Yield of isolated product based on **3a**.

However, by using 10 mol-% of base the yield of the product decreased to 66% (Table 2, entry 3). Once the optimal amount of base was established, the amount of diselenide was varied. The best condition was found to be 1 equivalent of indole (**1a**) to 1.5 equivalents of diselenide (**2a**), which provided the product in 99% yield (Table 2, entry 4). A decrease in the yield was observed if the reaction was conducted with 1 equivalent for both reagents (Table 2, entry 5). Even with the use of a small excess amount of diselenide, the preparation of 3-selenylindoles with this protocol is greener than its sulfur counterpart.[25]

With the best conditions in hand, the scope of the reaction was investigated (Table 3). First, the effect of different groups bound to the indole nucleus was evaluated through reaction of various indoles with diphenyl diselenide. The electronic character of both electron-donating and -withdrawing substituents in the 5-position of the indole did not affect substantially the performance of the transformation. For these cases, the reaction proceeded with different groups including, methoxy, bromo, and ester groups, and gave desired products **3b**–**d** in good to excellent yields. If 4-

Table 3. Synthesis of 3-selenylindoles.



cyanoindole was used, the corresponding product **3s** was obtained in 43% yield.

The presence of a phenyl substituent at the 2-position led to a decrease in the yield of product **3e** (61%). Substitution of hydrogen by a methyl group at the 1-position did not result in the formation of product **3t**, which suggests that this position contains the free amine (N–H).

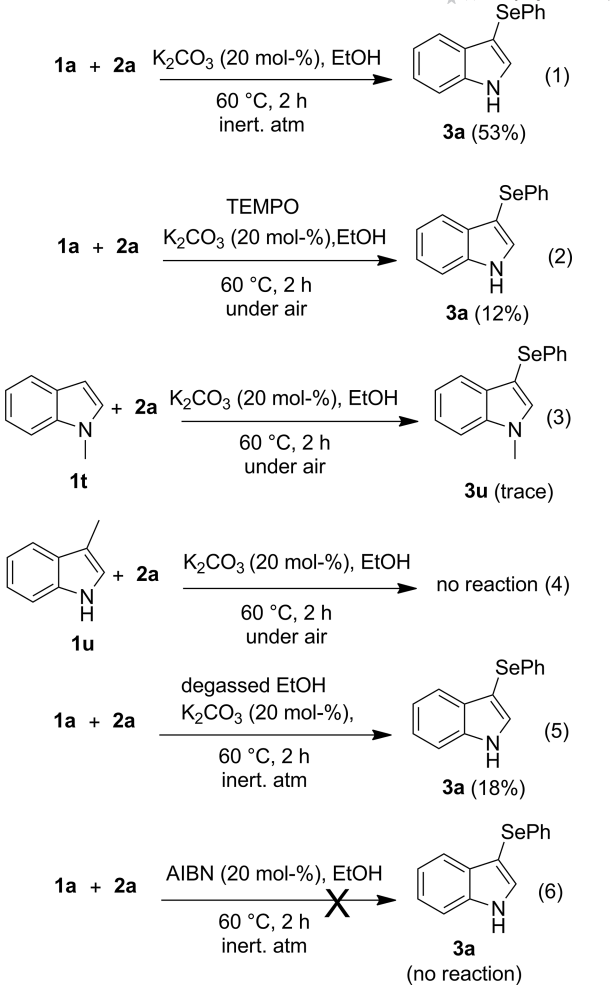
Next, we examined the influence of different diaryl diselenides. We observed that a substituent in the aryl moiety of these compounds did not have a great influence on the reactivity of the reaction. If diselenides containing electron-withdrawing groups (e.g., Cl, CF_3) were employed, corresponding products **3f**–**g** were obtained in quantitative yields. Electron-donating groups (e.g., Me, OMe) in the *ortho* and *para* positions also proved to be efficient under the reaction conditions, and corresponding products **3j**, **3h**, and **3o** were obtained in very good yields. By using a benzylic diselenide, a decrease in the yield of product **3i** was observed. The employment of an aliphatic diselenide did not result in the formation of product **3k**.

To demonstrate the versatility of the protocol developed, we performed this transformation with the use of indoles containing different substituents as well as diaryl diselenides. All multifunctionalized products synthesized (i.e., **3l**–**n**, **3p**–**r**) were obtained in good to excellent yields, which shows that the reaction has good functional group tolerance.

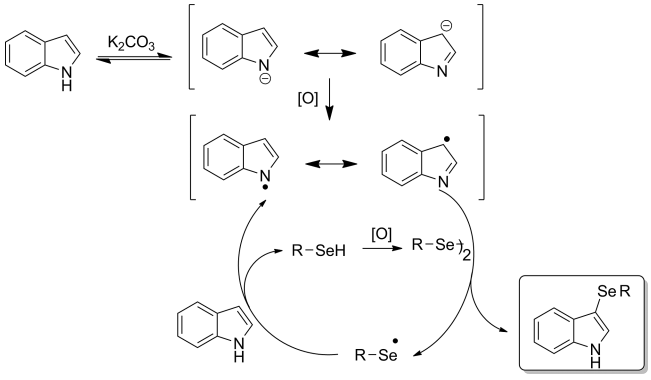
The mechanism of the C-3 substitution was investigated through control experiments, as shown in Scheme 1. In Equation (1), the reaction was performed under an inert atmosphere and yielded product **3a** in 53% yield, which indicated that the presence of oxygen was important for this transformation. We also evaluated the effect of a radical trap on the reaction outcome. If 2,2,6,6-tetramethylpiperidin-1-oxyl (TEMPO) was employed, we observed a significant decrease in the yield (12%), which indicated a radical pathway [Equation (2), Scheme 1]. The need for a free NH [Equation (3), Scheme 1] group suggested that this hydrogen is essential for the formation of the product. Finally, the reaction was conducted by using 3-methylindole to block the 3-position and to check its reactivity in this protocol. In this case, the formation of the corresponding product was not observed [Equation (4), Scheme 1].

We also performed another reaction [Equation (5), Scheme 1] under an inert atmosphere by using degassed ethanol. In this case, the yield dropped to 18%, which showed that oxygen was essential for the radical catalytic cycle proposed (Scheme 2). The reaction in the presence of the radical initiator 2,2′-azobisisobutyronitrile (AIBN, 20 mol-%) was also promoted [Equation (6), Scheme 1]. In this case, we did not observe the formation of the desired product. It is possible to conclude that K_2CO_3 is essential to promote the initiation step with the formation of the indole radical.

According to the literature[27] and on the basis of the experimental results, a proposed mechanism is represented in Scheme 2. Initially, the hydrogen atom attached to the nitrogen atom of indole is removed by K_2CO_3, which generates a negative charge on the indole. Subsequently, the indole radical is generated from the indole anion in the presence of atmospheric air. The indole radical reacts with diselenide to form the 3-selenylindole and a selenide radical. This species, in turn, removes the hydrogen atom from another indole molecule to complete the catalytic cycle, whereas the selenol is oxidized back to the diselenide.



Scheme 1. Investigation of the reaction mechanism.



Scheme 2. Proposed mechanism for the reaction.

Conclusions

In conclusion, we developed alternative greener methodology to obtain 3-selenylindoles, a class of compounds of interest for therapeutic applications, under mild conditions. It is important to note that ethanol was employed as a renewable biosolvent of low environmental risk and K_2CO_3 was used in catalytic amount. The methodology outlined herein allowed the synthesis of a library of 3-selenylindoles with different functionalities in yields of up to 99% in a short reaction time.

Experimental Section

General Procedure: A round-bottomed flask was charged with the indole (0.5 mmol), dichalcogenide (0.37 mmol), K_2CO_3 (20 mol-%), and ethanol (1 mL). The resulting solution was stirred at 60 °C for 2 h. The progress of the reaction was monitored by TLC. Upon completion of the reaction, the crude product was purified by column chromatography (silica gel, hexane/ethyl acetate) to furnish the pure product.

Acknowledgments

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