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Selenocyanation of Indoles Promoted by Visible Light †

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Abstract: We developed a promising synthetic methodology for the regioselective photocatalyzed 3-selenocyanation of indoles, employing potassium selenocyanate (KSeCN) and a blue LED light. The 3-selanylindoles have been emerging as a potentially bioactive class of compounds and already have demonstrated anti-inflammatory, antinociceptive and anticancer properties. There are in the literature several methodologies for their preparation; for example, applying intermolecular cyclization with Se-based electrophilic species. Therefore, it is of interest to seek innovative and effective methodologies to selectively access this class of molecules. Furthermore, the photocatalytically formed NCSe· radical can react directly with the *N*-heterocycle unsaturated substrates, affording the desired compound more effectively than other electrophilic selenium species. In addition, the 3-selenocyanato-1*H*-indole derivatives can be employed as precursor to obtaining diselenides, through a reduction–oxidation reaction sequence. The new method employs indole as unsaturated *N*-heterocycle substrate, and 1.3 equiv. of potassium selenocyanate as a selenium source, in the presence of 5.0 mol% of eosin Y, an organic photocatalyst, and 1.0 mL of acetonitrile. The system was stirred and irradiated with a blue LED light for 5 h, and the crude was purified using column chromatography. Thus, as a result, we developed an efficient and smoothly methodology to prepare 3-selenocyanato-1*H*-indole derivatives, in good yields.

Keywords: visible-light; indoles; selenium

1. Introduction

Heterocycles compounds are a privileged class of compound, widely found in the nature and very important in the pharmaceutical industry. Furthermore, the nitrogen and sulfur-containing derivatives have demonstrated great results in organic synthesis research as substrate [1]. Among them, indole is the most important derivative of the heterocyclic compounds, as it is the core motif of pivotal molecules in different biological systems. One remarkable example is the tryptophan, an essential amino acid, which is used to construct proteins and to deliver different neurotransmitters in the central nervous system [2]. Thus, based on the biocompatibility of this class of heterocycles, several indole derivatives have been employed against several pathologies, presenting, for example, anticancer, antiviral, and anti-inflammatory activities [2,3].

On the other hand, organochalcogen-containing compounds (sulfur and selenium) present pharmacological applications [4] and participate in several biologicals process, expressing important actions [5]. In this sense, molecular hybridization, between chalcogen-containing groups and *N*-heterocycles compounds, can promote a remarkable increase in the bioactive potential of these compounds. Thus, we disclose herein the photocatalyzed 3-selenylation of indoles, employing a blue

light LED as an alternative energy source and using potassium selenocyanate as a Se-based electrophilic specie.

2. Results and Discussion

Firstly, based on the literature [6,7], indole (**1a**) (0.3 mmol), potassium selenocyanate (**2**) (KSeCN, 1.3 equiv.), the organic photocatalyst eosin Y (5 mol%) and acetonitrile (MeCN, 1.0 mL) were added into the reaction flask. The resulting mixture was stirred for 5 h at room temperature under blue LED irradiation. At the end of the process, the desired product was obtained with 85% yield (Table 1, entry 1).

Table 1. Optimization of reaction conditions [a].

Entry	Photocatalyst (mol%)	Visible Light	Solvent	Yield (%) [b]
1	Eosin Y (5)	Blue LED	MeCN	85
2	Eosin Y (5)	Blue LED	THF	85
3	Eosin Y (5)	Blue LED	DCM	22
4	Eosin Y (5)	Blue LED	EtOH	18
5	Eosin Y (5)	Blue LED	Ethyl Acetate	81
6	Eosin Y (5)	Blue LED	DMSO	60
7	Eosin Y (5)	White LED	MeCN	73
8	Eosin Y (5)	Green LED	MeCN	70
9	Eosin Y (5)	45W-CFL	MeCN	66
10	Rose Bengal (5)	Blue LED	MeCN	91
11	Methylene blue (5)	Blue LED	MeCN	0
12	Eosin Y (10)	Blue LED	MeCN	82
13	Eosin Y (1)	Blue LED	MeCN	63
14	Rose Bengal (1)	Blue LED	MeCN	72

Reaction conditions: [a] into a specific reaction tube were added 0.3 mmol of indole (**1**), 1.3 equiv. of KSeCN (**2**), 5 mol% of organic photocatalyst, and solvent (1.0 mL). The mixture reaction was stirring for 5 h at the room temperature under visible light irradiation. The consumption of starting materials was monitored by TLC; [b] isolated yields obtained by chromatographic column.

Subsequently, different classical organic solvents were tested, including THF, DCM, EtOH, ethyl acetate and DMSO, to promote the reaction medium (Table 1, entries 2–5). Among them, the better results were obtained when THF and MeCN were employed, affording the desired product **3a** in 81% and 85% yield, respectively. However, MeCN was elected as the best solvente, as it is cheaper and greener than THF. Then, aiming to raise the reaction efficiency, the mixture was submitted to white and green light (50W LED) and to a 45W CFL; however, none of these measures afforded better results than the blue 50W LED (Table 1, entries 7–9).

Finally, several organic photocatalysts, in different catalytic loads, were tested (Table 1, entries 10–14). Among them, rose bengal (5 mol%) was efficient to deliver the product **3a** in 91% yield (Table 1, entry 10). However, due to high cost of rose bengal, eosin Y (5 mol%) was elected as the best photocatalyst. Thus, the best reaction condition was established by reacting the substrates **1a** and **2** in MeCN (1.0 mL), in the presence of eosin Y (5 mol%) as an organic photocatalyst, being the resulting system stirred for 5 h at room temperature, under blue LED irradiation.

3. Conclusions

In conclusion, we have developed a simple and efficient approach to access 3-selenocyanato-1*H*-indole, employing potassium selenocyanate as an efficient Se-based source. It is worth mentioning

that some studies are occurring in our laboratory, including the reaction substrate scope, as well as the search for evidence to clarify each step of the reaction mechanism.

4. General Information

The reactions were irradiated by blue LED light (50 W) and monitored by TLC carried out on pre-coated TLC sheets ALUGRAM® Xtra SIL G/UV254 by using UV light as a visualization agent and the mixture of 5% vanillin in 10% H_2SO_4 under heating conditions as a developing agent. Merck silica gel (particle size 63–200 μm) was used for flash chromatography. Hydrogen nuclear magnetic resonance spectra (^{1}H NMR) were obtained at 400 MHz on a Bruker Ascend 400 spectrometer. The spectra were recorded in $CDCl_3$ solutions. The chemical shifts are reported in ppm, referenced to tetramethysilane (TMS) as the external reference. Hydrogen coupling patterns are described as singlet (s), doublet (d), triplet (t), doublet of doublets (dd), and multiplet (m). Coupling constants (*J*) were reported in Hertz. Carbon-13 nuclear magnetic resonance spectra (^{13}C NMR) were obtained at 100 MHz on a Bruker Nuclear Ascend 400 spectrometer. The chemical shifts are reported in ppm, referenced to the solvent peak of $CDCl_3$

General procedure for synthesis of 3-selenocyanate-1*H*-indole compound **3a**: in a specific reaction tube was added 0.3 mmol of indole (**1a**), 1.3 equiv. of KSeCN (**2**), 5 mol% of photocatalyst eosin Y and 1.0 mL of MeCN. The reaction was stirred for 5 h at room temperature under blue LED visible light. After the reaction time, the solvent was completely removed under vacuum to give the crude product. The product was purified by column chromatographic using silica gel as the stationary phase and a mixture of ethyl acetate and hexane (40:60) as the mobile phase.

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