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Communication

# 3,3'-Selenobis(1-benzyl-2-oxo-1,2-dihydropyridine-4-carbaldehyde)

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**Abstract:** Selenium compounds have garnered significant attention in the field of medicinal chemistry due to their unique biochemical properties and potential therapeutic applications for different pathologies. In this study, we report the synthesis of a new selenylated bis-pyridone compound using SeO<sub>2</sub> as the source of selenium. The detailed characterizations <sup>1</sup>H and <sup>13</sup>C NMR and mass spectral analysis are given.

**Keywords:** selenium; pyridone; oxidation; heterocycle

## 1. Introduction

Selenium compounds have garnered significant attention in the field of medicinal chemistry due to their unique biochemical properties and potential therapeutic applications.[1,2] Selenium, an essential trace element, is crucial for the proper functioning of several enzymes and proteins, particularly those involved in antioxidant defense and redox regulation.[3,4] The incorporation of selenium into organic molecules has led to the development of novel compounds with diverse pharmacological activities, including antifungal, anticancer, antiviral, antimicrobial, and anti-inflammatory effects. [5,6,7,8] These compounds often exhibit enhanced efficacy and selectivity compared to their sulfur or oxygen analogs. As our understanding of selenium's role in human health deepens, the design and application of selenium-based therapeutics continue to expand, offering promising avenues for the treatment of various diseases.

The synthesis of organoselenium compounds has attracted a lot of interest in organic chemistry due to the unique chemical properties and biological activities of selenated compounds. Selenium, being chemically similar to sulfur, imparts distinct reactivity patterns that make its incorporation into organic molecules particularly valuable in synthetic strategies.[9,10] Gütlich et al. described a reaction between 3- and 3,5-substituted pyrazoles with selenium dioxide proceeds to afford bis(3R,5R0 -1H-pyrazol-4-yl)selenides in high yield (Figure 1).[11] Sawant et al. showed that mono- and di-selenylated bis-pyrazole derivatives could be obtained from arylated pyrazole in the presence of SeO<sub>2</sub> and DMSO as solvent. [12]

Continuing our research into the discovery of new antimycobacterials, [13,14,15,16] we have isolated an unusual selenium derivative as a by-product in an oxidation reaction. In this work, the synthesis and characterization of this compound is described.

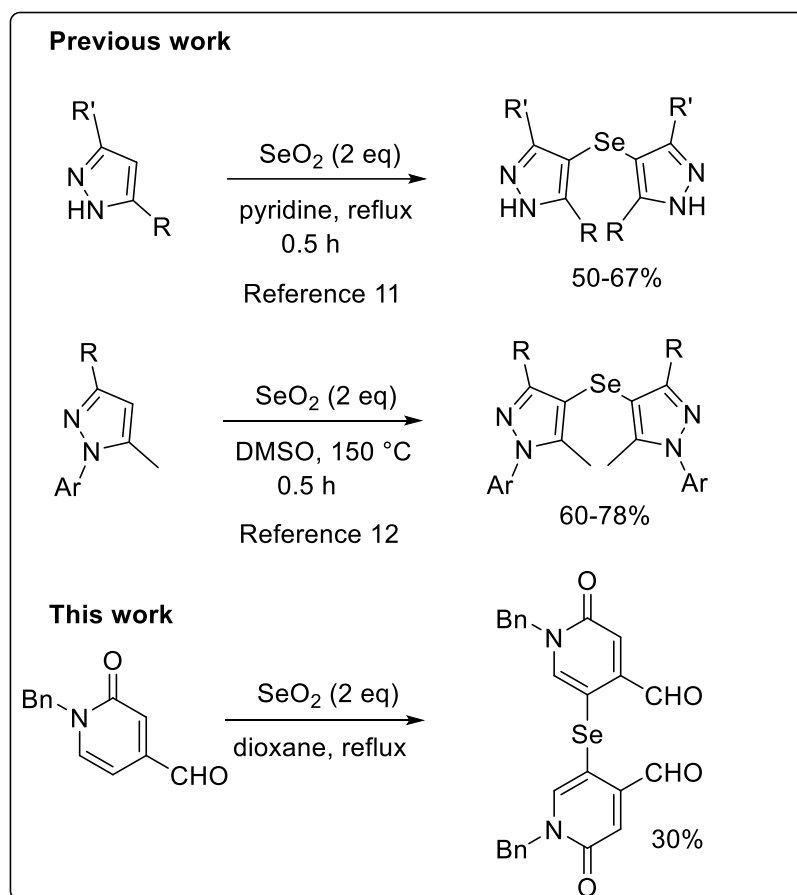
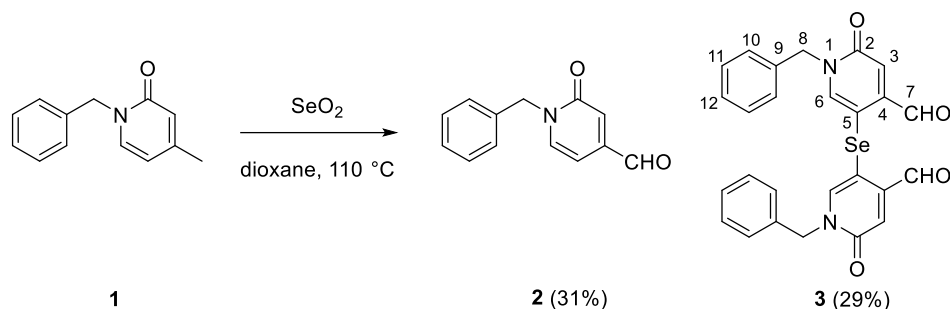


Figure 1. Examples of incorporation of selenium into organic compounds.

## 2. Results and Discussion

The synthesis of compound **2** involved the initial preparation of compound **1** (Scheme 1).[17] Then compound **1** was reacted with selenium oxide in dioxane at 110 °C to produce aldehyde **2** in 31% yield. During purification, another product was isolated in 29% yield which, on the basis of previous work and by comparison with the NMR of compound **2**, we have attributed to the structure of the selenylated product **3** (Scheme 1) [11,12]. Unfortunately, attempts to obtain suitable crystals of compound **3** for an X-ray structure determination using different solvents were not successful. Consequently, the structure was elucidated on the basis of  $^1\text{H}$  and  $^{13}\text{C}$  NMR analyses and mass spectrometry. The mass spectrum in negative mode of compound **3** showed a signal at  $m/z$  503.0524 matching the theoretical mass of the deprotonated molecule ( $M-H^+$ , 503.0510), with an additional signal at 549.0565 corresponding to the formic acid (used for the mass analysis) adduct ( $M-H^+/\text{HCOOH}$ , theoretical mass 549.0565), both signals displaying the typical pattern ( $^{76}\text{Se}$ , 9.37 %,  $^{77}\text{Se}$ , 7.63 %,  $^{78}\text{Se}$ , 23.77 %,  $^{80}\text{Se}$ , 49.61%,  $^{82}\text{Se}$ , 8.73 %) of molecules containing one selenium atom. Heteronuclear Single Quantum Correlation spectroscopy (HSQC) was used to assign  $^{13}\text{C}$  signals of compound **3** as shown in Table 1.

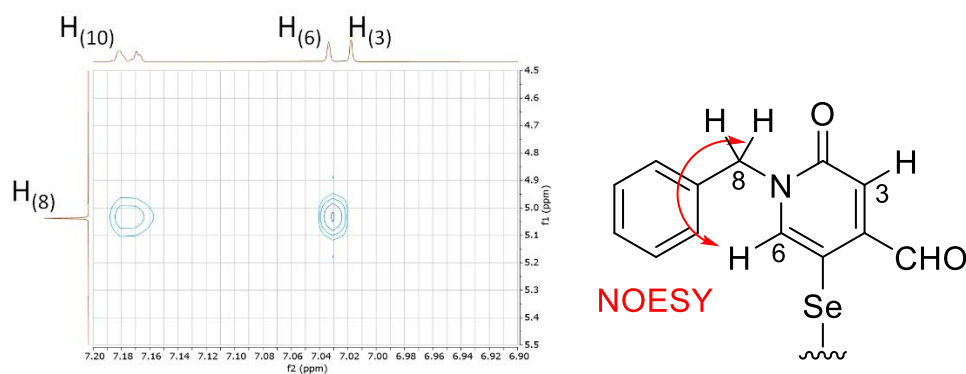
However, an ambiguity remained concerning the position of selenium on the heterocycle. On the  $^1\text{H}$ -NMR spectrum, the absence of coupling between the two protons of the heterocycle, which appear as singlets at 6.99 and 7.01 ppm, shows that selenium is not in position 3 on the ring. A correlation observed in the Nuclear Overhauser Effect spectroscopy (NOESY) spectrum between an heterocyclic proton (*i.e.*, H6 proton) and the benzylic protons (H8) leads to the conclusion that selenium should be located at position 5 (Figure 2).



**Scheme 1.** Synthesis of compound **2** along with the selenylated compound **3**.

**Table 1.**  $^1\text{H}$  and  $^{13}\text{C}$  chemical shifts (ppm) for compound **3**.

Position	$\delta_{\text{H}}$	$\delta_{\text{C}}$
2	---	161.40
3	6.99	126.06
4	---	143.05
5	---	103.00
6	7.01	141.28
7	9.86	191.78
8	5.01	52.31
9	---	134.48
10	7.15	128.81
11	7.36	129.32
12	7.31	128.95



**Figure 2.** 2D NMR –NOESY correlation observed for the CH<sub>2</sub> of the benzyl group and H-6 in compound **3**.

### 3. Materials and methods

All reagents and solvents were purchased from commercial sources (Sigma Aldrich or Alfa Aesar) and were used without further purification.  $^1\text{H}$ -NMR and  $^{13}\text{C}$ -NMR spectra were recorded on Bruker Advance 300 and 500 spectrometers, respectively, and the residual proton signals of deuterated  $\text{CDCl}_3$  were used as an internal reference ( $\delta = 7.26$  ppm and 77.00 ppm, respectively). Proton coupling patterns are abbreviated as “s” for singlet, “dd” for doublet of doublets and “m” for multiplet. The high-resolution mass spectrum (HRMS) was recorded on a Xevo G2 QTOF (Waters, Milford, USA).

#### Synthesis of compounds **2** and **3**:

To a 25 mL round bottomed flask containing the 1-benzyl-4-methylpyridin-2(1H)-one (0.25 mmol, 50 mg, 1 equiv.), were added selenium oxide (0.3 mmol, 33.3 mg, 1.2 equiv.) under argon

followed by anhydrous 1,4-dioxane (0.1 mL). The mixture was warmed up to reflux for 20 h, then cooled down at room temperature. Ethyl acetate was added and the resulting mixture was dried over magnesium sulfate and the solvent was concentrated under vacuum. The purification of the products was performed by using a 12 g prepacked column on a flash chromatography (25 mL/min, detector at 254 nm, 2 min at 40-60 petroleum ether – ethyl acetate, then gradient from 40-60 to 10-90 petroleum ether – ethyl acetate in 20 min).

**1-Benzyl-2-oxo-1,2-dihydropyridine-4-carbaldehyde (2)** – Lightly yellow powder (31%, 17 mg). <sup>1</sup>H-NMR (300 MHz, DMSO-D<sub>6</sub>): δ ppm 9.87 (s, 1H); 7.40-7.28 (m, 6H); 7.04 (dd, *J* = 1.8 Hz, 0.5 Hz, 1H); 6.55 (dd, *J* = 7.0 Hz, 1.9 Hz, 1H); 5.16 (s, 2H); <sup>13</sup>C-NMR (75 MHz, DMSO-D<sub>6</sub>): δ ppm 191.12; 162.64; 144.87; 138.55; 135.56; 129.03; 128.35; 128.21; 126.63; 101.05; 52.27; HRMS Calculated for C<sub>13</sub>H<sub>12</sub>NO<sub>2</sub> (ESI, M+H<sup>+</sup>): 214.0868. Found: 214.0873.

**3,3'-Selenobis(1-benzyl-2-oxo-1,2-dihydropyridine-4-carbaldehyde) (3)** – Orange powder (18.5 mg, 29%). <sup>1</sup>H-NMR (300 MHz, DMSO-D<sub>6</sub>): δ ppm 9.86 (s, 1H); 7.36 (m, 1H); 7.31 (m, 2H); 7.15 (m, 2H); 7.01 (s, 1H); 6.99 (s, 1H); 5.01 (s, 2H); <sup>13</sup>C-NMR (150 MHz, DMSO-D<sub>6</sub>): δ ppm 191.78; 161.40; 143.05; 141.28; 134.48; 129.32; 128.95; 128.81; 126.06; 103.00; 52.31; HRMS Calculated for C<sub>26</sub>H<sub>19</sub>N<sub>2</sub>O<sub>4</sub>Se (ESI, M-H<sup>+</sup> and M + HCOO<sup>-</sup>): 503.0510 and 549.0565. Found: 503.0524 and 549.0565.

**Supplementary Materials:** The following supporting information can be downloaded at the website of this paper posted on Preprints.org, <sup>1</sup>H, <sup>13</sup>C spectra of compound **2**; <sup>1</sup>H, <sup>13</sup>C, COSY, HSQC, NOESY spectra of compounds **3**; HRMS spectrum of compound **3**.

**Author Contributions:** EG: Investigation, Writing – original draft; JR: Investigation; SAA: Investigation; JAD: Investigation; PH: Investigation, Writing – review & editing; CL: Conceptualization, Investigation, Writing – review & editing.

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**Conflicts of Interest:** The authors declare no conflicts of interest.

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