Iraqi Journal of Natural Sciences and Nanotechnology IJNSN

Journal Homepage : https://publications.srp-center.iq/index.php/ijn

# Synthesis and Characterization of Some New Bis (1,3-selenazole) from Bis-Selenocarboxamide

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**Keywords:**

*Organoselenium compounds, aryl-selenocarboxylic, bis(1,3-selenazoles).*

**Abstract**

The synthesis of new bis (1,3-selenazoles) was achieved by subjecting primary bis aryl-selenocarboxylic amides to cyclization with α-bromoketones. The methodical preparation of bis (1,3-selenazoles) was achieved by the primary bis selenoamides with α-halo ketones. Bis selenoamides were gained from the reaction of NaHSe with aryl nitrile. The resulting bis (1,3-selenazoles) has been characterized by different spectroscopic methods; such as $^{1}H$ ,$^{13}C$ NMR, IR, and mass spectroscopic data to prove the structural formula of the prepared compounds.

## Introduction

Research interest in Se-containing five-membered rings has made extremely quick progress in recent years due to their applications in organic synthesis and drug discovery. Hofmann G first reported selenazoles in 1889, featuring a unique ring structure with one Se and one N atom. The prevalence of selenazoles in pharmaceutically active compounds has fueled significant investigation into their synthesis and biological properties. Notably, 1,3-selenazoles (characterized by two double bonds and a 3-position N) stand out for their intriguing pharmacological potential, making them a hotspot for further research [1]. Several types of selenium-nitrogen heterocyclic compounds, which include selenazoles, selenazolidines, and selenadiazoles, are useful in organic synthesis and biology. These compounds have been studied for their antioxidant, enzyme-inhibiting, and anti-microbial properties[2]. Selenazoles are a group of heterocyclic chemical substances which belong to the group of azoles. Selenazoles members are five-membered cyclic organic compounds that carry selenium and

a nitrogen atom in the ring structure. The parent systems form selenazole (more precisely: 1, 3-selenazole) and isoselenazole (more precisely: 1, 2-selenazole) [3]–[5].

1,3-Selenazoles are valuable drug candidates due to their antibiotic and anti-cancer properties [6]. They have shown promising biological activity that attract significant research interest. Various methods have been developed to synthesize these molecules, with the Hantzsch condensation being a popular choice. This approach, which was first described in 1889, allows for the preparation of diverse 1,3-selenazole derivatives by selecting appropriate starting materials [7]. While many syntheses rely on primary selenoureas and selenoamides, these key building blocks are often difficult to obtain, and limitations exist in current synthetic procedures [8].

In this study, new bis (1,3-selenazoles) was successfully synthesized through react bis aryl-selenocarboxylic amides with alpha-bromoketones. The systematic preparation of bis (1,3-selenazoles) involved the reaction of primary bis selenocarboxamides with alpha-halo ketones. Bis selenoamides were derived from the reaction of NaHSe with aryl nitrile. The structural formula of the prepared compounds was confirmed through various spectroscopic methods, including $^{1}H$, $^{13}C$ NMR, IR, and mass spectroscopic data.

## Experimental procedure

### Main Devices

Nuclear magnetic resonance (NMR) spectroscopy was performed using a 400 MHz Bruker AVANCE NEO 400 spectrometer at the Department of Chemistry, College of Education for Pure Science, University of Basrah. Samples were dissolved in either deuterated dimethyl sulfoxide or deuterated chloroform with tetramethylsilane as the refer ace. Chemical shifts for both $^{1}H$ and $^{13}C$ NMR spectra were reported in delta units relative to TMS.

### Synthesis

All reactions were achieved under inert Argon atmosphere. All the used solvents have been dried and freshly distilled under Argon before use.

### Synthesis of 1, 4-bis (chloromethyl)-2, 5-dimethylbenzene (1)

This compound was prepared according to a literature method [9] as follows: (10g; 0.001mol) of p-xylene mixed with (72g; 0.0023 mol) of 35% formaldehyde and (115 ml) of conc. Hydrochloric acid the mixture refluxed for 5h the resulting solution cool in the refrigerator overnight. Then filtrated, the precipitate washes off with water until neutralization. The off-white gelatinous product was washed off with n-hexane to obtain a white solid compound.

**Synthesis of 2,2'-(2,5-dimethyl-1,4-phenylene) diacetonitrile (2)**

This Compound was prepared by the method reported in the literature [10], [11]. To a stirred suspension of potassium cyanide (1.9 g; 30.0 mmol, 2.5 equiv.) in 50 ml dimethyl sulfoxide (DMSO) was added 1,4-bis (chloromethyl)-2,5-dimethylbenzene (2.4g; 12 mmol, 1.0 equiv.) in small portions consecutively at 50 $^0$C. The mixture was kept at 50 $^0$C for 1 hour after the addition of 1,4-bis (chloromethyl)-2,5-dimethylbenzene and then it was heated at 85 $^0$C for 5 min. After cooling to about 40 $^0$C, the mixture was extracted with toluene and washed with brine to obtain the desired product, which was then recrystallized from ethanol.

**Synthesis of 2, 5-dimethylbenzene-1, 4-bis (selenocarboxamide) (3):**

NaBH4 (2.02g; 53.75mmol) was added portion-wise over 30 min to a suspension of Se powder (3.95g; 50mmol) in (50ml) ethanol under Argon atmosphere while hydrogen evolved vigorously. The resulting solution was stirred for a further 15 minutes. Pyridine (8.1ml; 100mmol) and 2,2'-(2,5-dimethyl-1,4-phenylene) diacetonitrile (1.84g; 10mmol) were then added to NaHSe and the solution was refluxed while HCl (25ml; 2M) was added dropwise over 3h. The resulting solution was refluxed for an additional 30 minutes then allowed to cool to room temperature and saturated aqueous solution of $Na_2CO_3$ (25ml) and $H_2O$ (50ml) were added, filtered and the precipitate was washed with $H_2O$ then dried, and collected as a stable pale-yellow product**.**

**Synthesis of bis (1,3-selenazole) (4) , (5) and (6)**

To a solution of (1 mmol) 2, 5-dimethylbenzene-1, 4-bis (carboselenoamide) in EtOH (50ml) was added (2 mmol) of alpha bromoketone dropwise. The mixture was refluxed for 45 min, then neutralize the mixture by 10% aqueous ammonia, the resulting mixture was extracted with $CH_2Cl_2$ (3x20 ml). The organic layer was washed with water, dried with sodium sulfate, and the solvent removed to give the pure diselenazole compound.

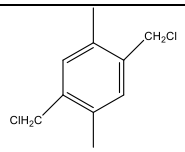
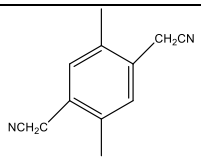
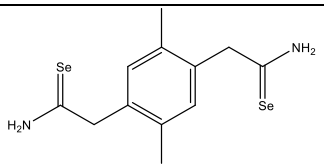
**Results and discussion**

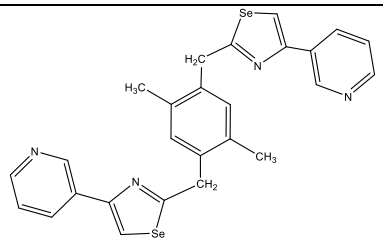
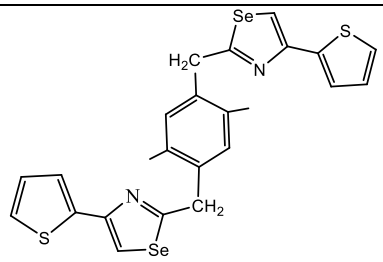
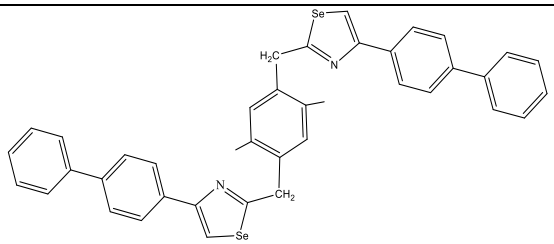
The first part of this work includes the preparation of 2,2'-(2,5-dimethyl-1,4-phenylene) diacetonitrile (2). This compound has been prepared starting from para-xylene by the reaction of chloromethylation to produce 1, 4-bis (chloromethyl)-2, 5-dimethylbenzene (1). The last compound has been reacted with KCN to afford the target compound of (2), see scheme 1. compound (3) has been prepared according to the literature, where the preparation reaction of this compound was carried out as follows: 1 mole of dinitrile has been refluxed with 2 moles of aluminum selenide in EtOH to give diselenocarboxamide. Some modification has been carried out on the previous procedure, where the dinitrile; 1 mole was reacted with 4 moles of NaHSe to give diselenocarboxamide (5), see scheme 1 and table 1.

Due to the instability of aliphatic and aromatic selenoamides and the challenges associated with their purification, coupled with our objective of synthesizing novel heterocyclic selenium compounds, we have prepared a new series of bis (1,3-selenazole) heterocycles compounds. To achieve this goal, selenocarboxamide 3 was subjected to reaction with two molar amounts of α-halo ketones (namely, 3-(Bromoacetyl) pyridine, 2-(Bromoacetyl) thiophene, and 2-Bromo-4-phenyl acetophenone). The reaction of selenocarboxamide 3 with α-halo ketone (3-(Bromoacetyl) pyridine, 2-(Bromoacetyl) thiophene, 2-Bromo-4-phenylacetophenone) in a 1:2 molar ratio affords dicyclic selenazoles (4), (5) and (6) as shown in scheme 1.

Figure 1 shows the infrared spectra of compound (3). This figure demonstrates the disappearance of the C≡N stretching peak, ranging between 2255-2215 $cm^{-1}$, in nitrile compound. Additionally, strong bands emerge, attributed to the ῡ (N-H) vibrations encompassing both asymmetrical and symmetrical stretching within the 3252 $cm^{-1}$ and 3113 $cm^{-1}$ ranges, respectively. The spectra exhibit a band ranging from strong to weak 1612 $cm^{-1}$, signifying the bending vibration of N-H [62]. Furthermore, the IR spectra of compounds 3 illustrate a band in the range of 1442 cm-¹, designated to the C=Se stretching contribution [51]. These assignments agree well with the previously reported values and closely resemble those of aliphatic and aromatic selenoamides [12][12].

Table 1: structures and some physical properties of the prepared compounds (1-6)

| Comp. | Structure | Color | m.p. (ºC) | Yield% |
|---|---|---|---|---|
| **1** |  | white | 102-104 | 75 |
| **2** |  | white | 152-155 | 65 |
| **3** |  | pale-yellow | 219-220 | 80 |

| Comp. | Structure | Color | m.p. (ºC) | Yield% |
|---|---|---|---|---|
| **4** |  | Red-orange | 207- 208 | 80 |
| 5 |  | Off-white | 195-196 | 72 |
| **6** |  | Pale yellow | 229-230 | 75 |

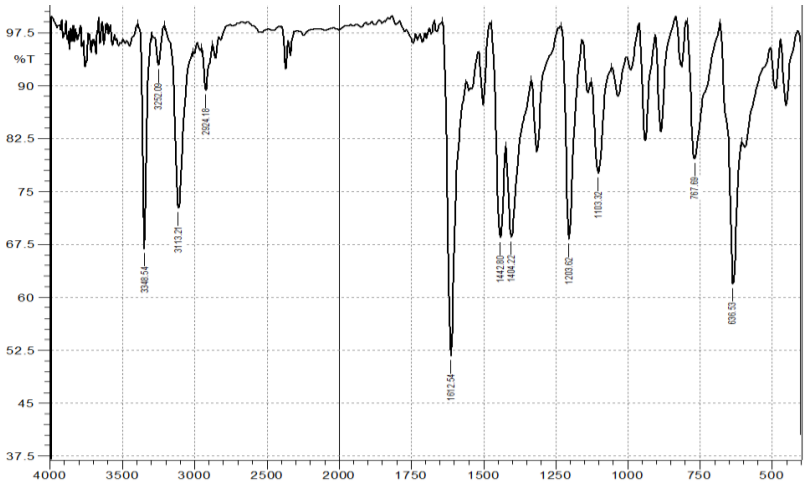



**Figure 1: FTIR spectrum of compound 3**

The FTIR spectra of bis 1,3-selenazoles compounds (4-6), see figure 4, indicate the disappear of all ῡ (N-H) and ῡ (C=Se) vibrations and the appearance of a strong to weak band in the range 1597-1504 $cm^{-1}$ owing to ῡ (C=N), the ῡ (C-Se) stretching vibration observed in the region 621-555 $cm^{-1}$.

Additionally, the vibrations of (C-H) bond for the heterocyclic ring are observed in the range 3082-3024 $cm^{-1}$ which is an attribute of hetero-aromatic ring, this indicates the conversion of the selenoamide group to selenazoles [13].

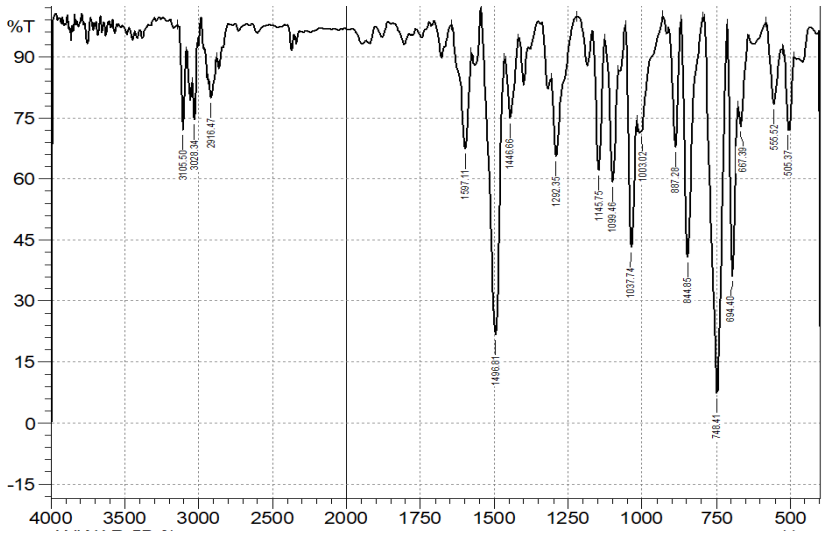



**Figure 2: FTIR spectrum of compound 4**

The $^{1}H$ NMR spectra were recorded in DMSO-d6 or $CDCl_3$. The chemical shifts are reported in ppm referenced to TMS. The spectrum of compound (3), shown in figure 3, shows all the expected peaks with the proper intensity ratio. The spectra show two signals downfield in the range of 9.82 to 10.46 ppm due to the carboxamide group [14]. The appearance of these two signals at a lower field could be attributed to the slow rotation of the selenoamide bond. The aromatic protons appear as sharp signals in the range of 7.02 ppm. Furthermore, the signals of methyl and methylene groups appear at 3.84 and 2.22 ppm respectively as a sharp singlet signal. The $^{1}H$-NMR spectra of bis 1,3-selenazoles compounds indicated that the expected peaks includ sharp singlet signals between 8.02 and 8.84 ppm assigned to the only proton of the 1,3-selenazole rings. Thus, it may be concluded that as the s character increases in $sp^2$, bonding electrons move closer to carbon thereby deshielding the protons. This result is supported by the literature data [15],[16]. A singlet to multiplet signal appears at the range 7.07-9.23 ppm for the aromatic protons. For the spectrum of compounds (3) (4) and (5) the aliphatic protons resonate as a sharp singlet at 4.33, 4.27 and 4.34 ppm for the methylene group and at 2.27, 2.26, and 2.30 ppm for the methyl group.

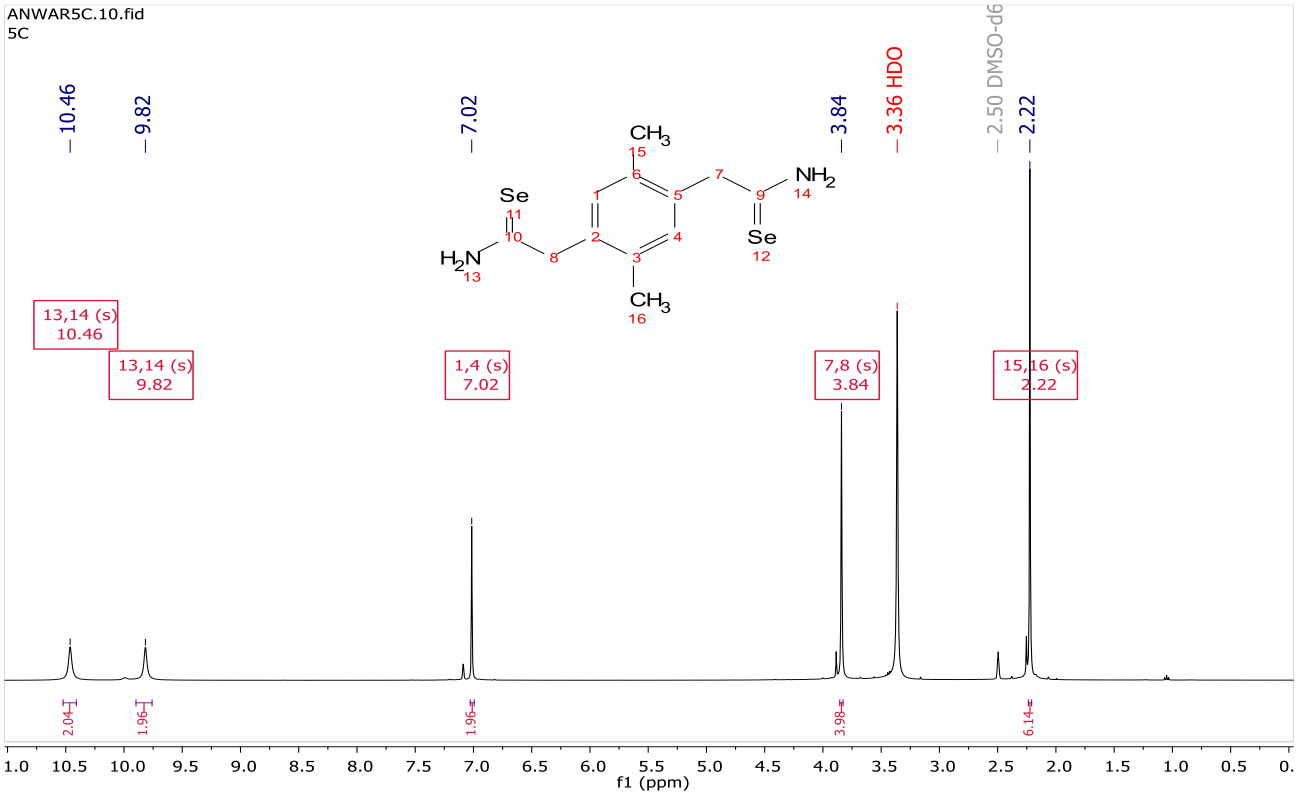


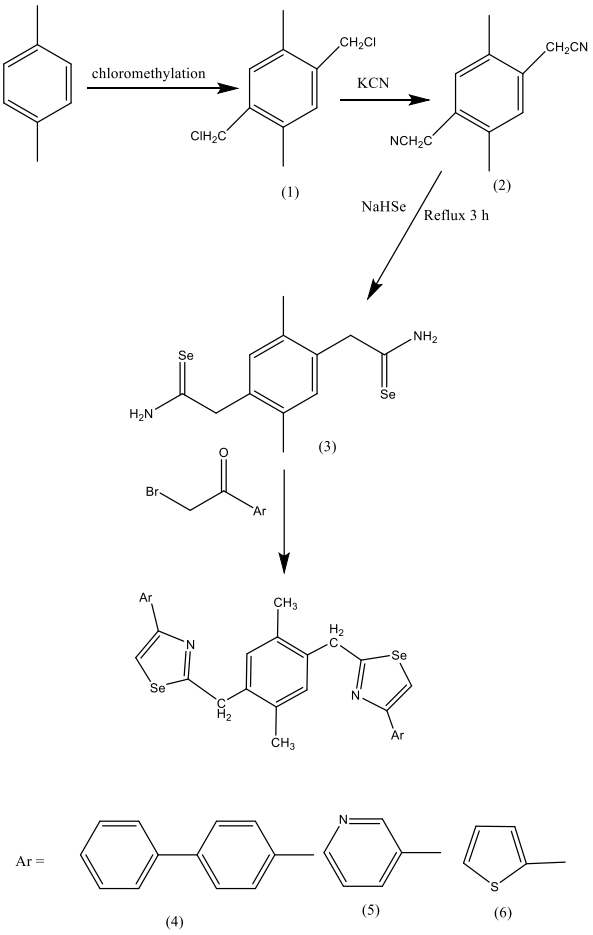

**Figure 3: 1H NMR spectrum of compound 3**

Structures of the selenazoles were supported by the $^{13}$C-NMR data in a way that agrees with the related values [17],[18]. The $^{13}$C NMR spectra of new selenazoles were all measured in $CDCl_3$ or $d^6$-DMSO. The $^{13}$C-NMR spectra possess three signals characteristic for the bis 1, 3-selenazole rings along with the predictable signals from the aromatic carbon backbones. The signal of Se-C=N of the selenazole ring appears at the low field of 170.25- 178.76 ppm, while the C-Se signal appears at the higher field in the range of 117.60-127.32 ppm. This may be attributed to the shielding influence of the selenium atom. The signals for an aromatic substitute in the selenazole rings appear at a range of 121.46 - 152.94 ppm. In compounds (1) and (2), the signal of aliphatic carbon of the methyl group appears at 18.77 and 18.73 respectively, while the signal of methylene overlaps with the signal of the solvent (DMSO).

## Conclusion

In conclusion, our study successfully accomplished the synthesis of novel bis (1,3-selenazoles) through the reaction of bis aryl-selenocarboxylic amides and alpha-bromoketones. The systematic preparation of these bis (1,3-selenazoles) was achieved by reacting primary bis selenoamides with α-halo ketones. The precursor bis selenoamides were obtained through the reaction of NaHSe with aryl nitrile. The structural elucidation of the synthesized compounds was confirmed using many spectroscopic

techniques, including $^{1}H$ NMR, $^{13}C$ NMR, IR, and mass spectroscopy. These analyses provided conclusive evidence to support the proposed structural formulas for the synthesized bis(1,3-selenazoles). The successful completion of this synthetic approach and the comprehensive characterization of the products contribute valuable insights to the field of selenazole chemistry and open avenues for further exploration and application of these compounds in various scientific and industrial domains.




**Scheme (1) Synthesis of (1) - (6) compounds**

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