

Synthesis And Characterization Of Diselenide Derivatives Of 4-Substituted-N,N-Diisopropylpyridine-2-Carboxamide : X-Ray Structure Of Bis(3-(4-Chloro-N,N-Diisopropylpyridine-2-Carboxamide)) Diselenide

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ABSTRACT

The lithiation of 4-substituted-N,N-diisopropylpyridine-2-carboxamide (**1a/1b/1c**) and its application in the synthesis of diselenide derivatives was investigated. **1a**, **1b** and **1c** were lithiated with 2 equiv. of *n*-BuLi or LDA at -78°C . Addition of elemental selenium to the carbanion led to the formation of corresponding selenolate anions respectively. The selenolate anions were aerial oxidized to afford the corresponding diselenides. The prepared compounds have been characterized by single crystal X-ray crystallography, NMR (^1H , ^{13}C and ^{77}Se), FTIR, elemental analysis and Mass spectroscopy. Crystal structure of bis(3-(4-chloro-N,N-diisopropylpyridine-2-carboxamide)) diselenide (**3a**) reveals an intramolecular secondary 1,4-type Se/Cl interaction.

Keywords

Organochalcogen, Diselenide, Lithiation

1. INTRODUCTION

The field of organochalcogen chemistry throws numerous challenges to the present day chemists as these compounds are unstable and difficult to synthesize. There have been numerous reports to show that organochalcogenides can be stabilized by attaching a chelating group in a close proximity to the chalcogen atom. The presence of $\text{E}\cdots\text{X}$ (N/O/Cl) secondary interactions have been shown to be responsible for the increase in the stability of these compounds [1], [2], [3]. The concept of secondary/non-covalent interactions was introduced by Alcock [4]. These interactions were defined as an interaction between two atoms when distance between them is longer than the sum of covalent radii but shorter than the sum of the van der Waals radii of the corresponding atoms. X-ray crystallographic techniques are used as an evidence for existence of secondary interactions in a large number of organochalcogens [5], [6], [7].

Organochalcogen compounds containing $\text{E}\cdots\text{X}$ (N/O/Cl) secondary interactions have shown tremendous application in and as enzyme mimetics [8], ligands for metal chalcogenolates that serve as excellent single source precursors for semiconducting materials [9], synthesis of Schiff base macrocycles that contain selenium and tellurium atoms [10], stabilization of folded protein structures [11], a tool in supramolecular chemistry [12], and in the regulation of enzymatic functions [13].

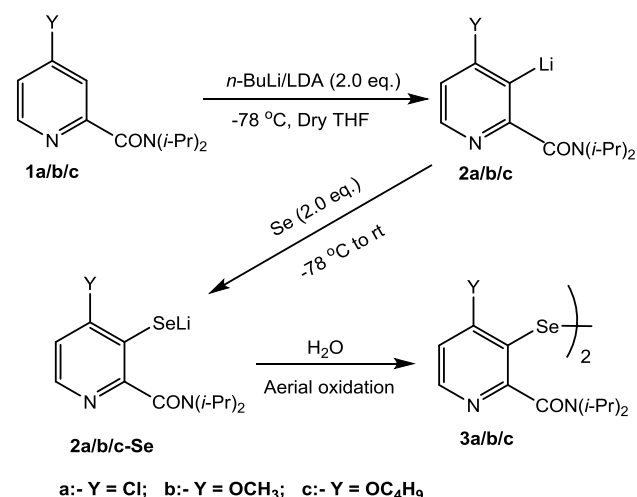
The chemistry of internally chelated organochalcogens with the chalcogen atom attached to the benzene ring has been extensively studied, however the corresponding pyridine chemistry is relatively under explored [14]. Therefore, effort

was made to synthesize internally chelated diselenide compounds derived from 4-substituted-N,N-diisopropylpyridine-2-carboxamide (**1a-1c**).

2. RESULTS AND DISCUSSION

2.1 Preparation of Diselenide Derivatives

SCHEME 1. Synthesis of diselenides of **1a/1b/1c**



Reaction of **1a** or **1b** or **1c** (a light yellow clear solution in dry THF) with 2.0 equiv of *n*-BuLi at -78°C followed by stirring for another two h at -78°C resulted in the formation of a dark reddish brown solution of carbanion (**2a/2b/2c**). The solution was then treated with elemental selenium at -78°C . The reaction mixture was slowly brought to room temperature and stirred till complete dissolution of selenium was achieved. The complete dissolution of selenium indicated the insertion of selenium atom into the C-Li bond leading to the formation of the corresponding selenolate anion (**2a-Se/2b-Se/2c-Se**). The selenolate anion, upon hydrolysis and subsequent aerial oxidation offered the corresponding diselenides (**3a/3b/3c**) in good yields (Scheme 1, Table 1 entries 1-3).

In another attempt, LDA was used as a lithiating agent to affect the deprotonation of **1a/1b/1c**. LDA was cannulated into a solution of **1a/1b/1c** in THF at -78°C and reaction mixture was stirred for another 2 h. The resulting solution of carbanion was more intensely coloured than the carbanion obtained in case of *n*-BuLi. The anionic species was then treated with selenium powder and the resulting selenolate anion was subjected to aerial oxidation (Scheme 1). It was found that the yields of the corresponding diselenides

obtained with LDA were 5-10% more than that obtained with *n*-BuLi (Table-1, entries 4-6).

Table 1. Comparison of yields of diselenide of 1a-1c

Entry	Substrate	Base	Product (Yield %)	Yield (%)
1.	1a	<i>n</i> -BuLi	3a	65
2.	1b	<i>n</i> -BuLi	3b	61
3.	1c	<i>n</i> -BuLi	3c	62
4.	1a	LDA	3a	70
5.	1b	LDA	3b	68
6.	1c	LDA	3c	68

2.2 Spectral Studies

All the synthesized compounds were characterized by multinuclear NMR (^1H , ^{13}C and ^{77}Se), IR and Mass spectral techniques. Full spectral data of all the synthesized compounds have been given in experimental section. One of the compounds is also analyzed by single crystal X-ray diffractometer.

2.2.1 ^1H NMR Studies

The ^1H NMR spectra of 4-substituted-N,N-diisopropylpyridine-2-carboxamide chalcogen compounds have been taken in CDCl_3 with tetramethylsilane as the internal standard. The ^1H NMR spectra of 4-chloro-N,N-diisopropylpyridine-2-carboxamide (**1a**), 4-methoxy-N,N-diisopropylpyridine-2-carboxamide (**1b**), 4-butoxy-N,N-diisopropylpyridine-2-carboxamide (**1c**), shows three signals in the aromatic region with two doublets (H-6) and (H-3) and the third signal is a doublet of doublet at (H-5). The ^1H NMR spectra of diselenide compounds (**3a-3c**) shows two doublets in the aromatic region. The absence of the third signal clearly indicates the deprotonation of the pyridine ring at the C-3 position. The signals corresponding to H-6 in compounds **3a** slightly shifts upfield when compared to the signal in **1a**. The spectra contains two multiplets due to two non-equivalent $-\text{CH}(\text{CH}_3)_2$ groups and two doublets corresponding to two non-equivalent isopropyl methyl groups. This suggests restricted rotation about the C–N bond due to resonance leading to the double bond character between carbon and nitrogen in the molecule.

2.2.2 ^{77}Se NMR Studies

Diphenyl diselenide is used as the reference standard in all the ^{77}Se NMR experiments. The ^{77}Se NMR spectra of diselenides (**3a**, **3b** and **3c**) displayed a signal in the range of δ 366 to 444 ppm. The selenium signal in the spectrum of **3a** appears most downfield at δ 444.2 ppm when compared to **3b** at δ 369.5 ppm and **3c** at δ 366.0 ppm. This is probably due to the replacement of the chloro atom with an alkoxy group. The change of butoxy group in **3c** by methoxy group in **3b** has a very little effect on ^{77}Se signal.

2.2.3 X-RAY Crystallographic studies

In order to understand the structural details, crystals of one of the compounds have been grown and analyzed by single crystal X-ray diffractometer. Single-crystal X-ray data were collected using graphite-monochromated Mo K α radiation ($\alpha = 0.71073 \text{ \AA}$) on “Bruker SMART APEX CCD diffractometer” at 100 K. The linear absorption coefficients, scattering factors for the atoms and the anomalous dispersion corrections were taken from the International Tables for X-ray Crystallography [15]. The program SMART [16] was used for collecting frames of data, indexing reflections, and determining lattice parameters. The data integration and reduction were processed with SAINT [16] software. An empirical absorption correction was applied to the collected reflections with SADABS [17] using XPREP [18].

TABLE 2. Crystal data collection and structure refinement parameters of compound 3a

Compound	3a
Empirical formula	$\text{C}_{24}\text{H}_{32}\text{Cl}_2\text{N}_4\text{O}_2\text{Se}_2$
Crystal system	Orthorhombic
Space group	Pbca
a	12.2765 (6) \AA
b	12.8948(7) \AA
c	17.7098(8) \AA
α	90°
β	90°
γ	90°
Volume	2803.51 \AA^3

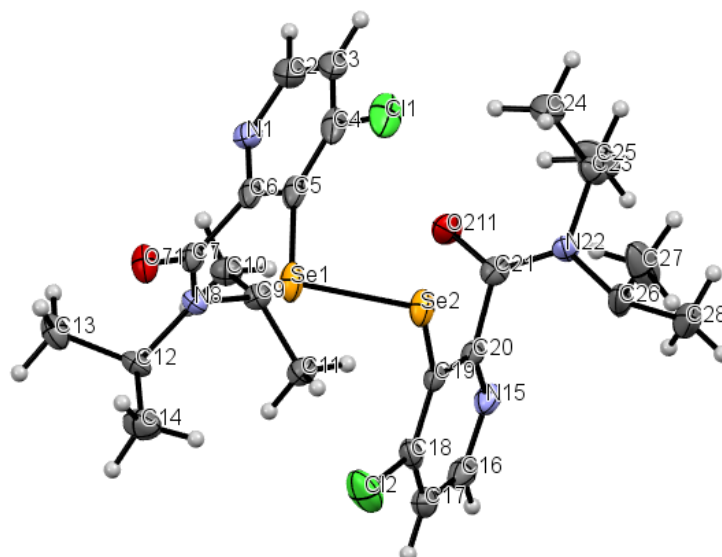


FIG 1 : ORTEP view of 3a showing an atom numbering scheme

All the structures were solved by the direct method using the program SHELXS-97 and were refined on F2 by the full-matrix least-squares technique using the SHELXL-97 [19] program package. All non-hydrogen atoms were refined with anisotropic displacement parameters in all the structure. Figure 1 shows the molecular geometry and the crystallographic numbering scheme of **3a**. The crystal data collection and structure refinement parameters of this compound has been given in Table 2. Selected bond lengths and angles are listed in Table 3.

TABLE 3. Selected bond distances (Å) and angles (°) for **3a**.

Bond lengths			
Se(1)–Se(2)	2.3338(5)	Se(1)–C(5)	1.936(4)
Cl(1)–C(4)	1.733(4)	Cl(2)–C(18)	1.735(4)
Bond angles			
C(5)–Se(1)–Se(2)	100.8(1)	C(2)–C(3)–H(3)	120.9
N(1)–C(1)–Se(1)	116.7(4)		

Short intramolecular contacts are also observed between Se(2) ...Cl(1) but the atomic distance between Se(1) ...Cl(2) is greater than the sum of their van der Waals radii. Short intramolecular contacts are also observed between some other atoms (Table 4, Fig. 2).

In addition to short intramolecular contacts, short intermolecular contacts were also observed between some atoms (Table 4). The diselenide **3a** shows a *cis* geometry with bond angles between Se(1)–C(5)–C(6) is 117.9° and between Se(2)–C(19)–C(20) is 119.3°.

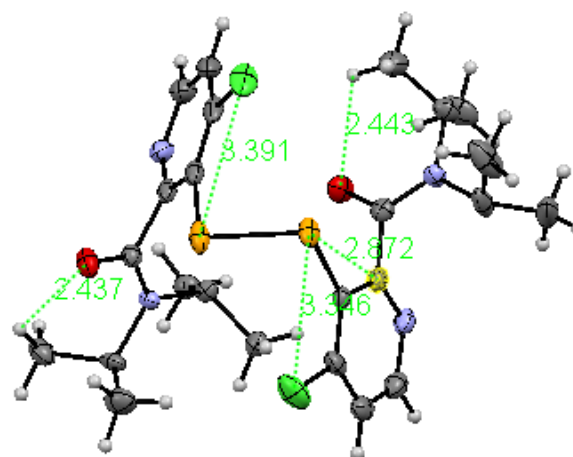


FIG 2 : Molecular structure of 3a exhibiting intramolecular secondary interactions

An interesting aspect in the structure of **3a** is the presence of intramolecular secondary 1,4-type Se/Cl interaction. The Se(1) ...Cl(1) atomic distance is 3.391 Å and Se(2) ...Cl(2) atomic distance is 3.461 Å, and these distances are significantly shorter than the sum of their van der Waals radii of 3.65 Å.

3. CONCLUSION

Synthesis of diselenide compounds derived from **1a**, **1b** and **1c** has been achieved by a method involving lithiation of **1a**, **1b** and **1c** with LDA/*n*-BuLi. The yield of the reaction involving the use of LDA is better than that obtained in case of *n*-BuLi. The single crystal X-ray structures of **3a** establishes the presence of intramolecular secondary 1,4-type Se/Cl interaction. The synthesis of these internally stabilized organoselenium compounds reported in the present research work will considerably contribute to develop antioxidants as internally stabilized organoselenium compounds have shown much better antioxidant properties since they form stable intermediates during the process involving the removal of oxidants.

TABLE 4. Shorter intramolecular and intermolecular bond distances (Å) for 3a. (value in parenthesis are the sum of their van der Waals radii)

Intramolecular Bond Distances			
Se(1) ...Cl(1)	3.391(3.65)	Se(2) ...Cl(2)	3.346(3.65)
Se(2) ...Cl(1)	3.439(3.65)	O(7 1) ...H(13 A)	2.437(2.72)
O(21 1) ...H(24 A)	2.443(2.72)	C(6) ...Se(1)	2.874(3.60)
Intermolecular Bond Distances			
O(71) ...H(11C)	2.556(2.72)	O(71) ...H(10A)	2.612(2.72)
O(17) ...H(211)	2.423(2.72)	C(17) ...O(211)	3.132(3.22)

4. EXPERIMENTAL

4.1 General

All the reagents and solvents were purified and dried by standard techniques [20] and deoxygenated by bubbling oxygen free dry nitrogen gas prior to use. Nitrogen gas was dried by passing through the terrain of anhydrous calcium chloride, potassium hydroxide, phosphorous (V) oxide and molecular sieves. ¹H NMR and ¹³C NMR spectra were recorded on Bruker 400 MHz spectrophotometer in CDCl₃ using tetramethylsilane (TMS) as an internal standard with chemical shift (δ) expressed in ppm downfield of TMS. The following abbreviations have been used while presenting the data: s-singlet, d-doublet, t-triplet, q-quartet and m-multiplet, dd-doublet of doublets. ⁷⁷Se NMR spectra were recorded in CDCl₃ using diphenyl diselenide as external standard on Bruker AC, 400 MHz spectrometer. The ESI mass spectra were taken on Water Q-TOF Micro spectrometer. Carbon, hydrogen, and nitrogen were estimated micro analytically on Vario MICRO Elemental analyzer. Infrared spectra were recorded between KBr pellets on a Perkin-Elmer Model 1430. Compounds **1a**, **1b** and **1c** were prepared by literature method [21].

4.2 Lithiation of 1a, 1b, 1c

4.2.1 n-BuLi as a lithiating agent

A flame dried three-necked 100 mL RBF was charged with **1a** (0.96 g, 4 mmol, 1.0 equiv)/ **1b** (0.94 g, 4 mmol, 1.0 equiv)/ **1c** (1.1 g, 4 mmol, 1.0 equiv) and dry THF (50 mL). The whole solution was cooled to -78 °C and n-BuLi (6.04 mL, 8 mmol, 1.39 N in hexane, 2.0 equiv) was added slowly to it. The resulting reddish brown solution of the carbanion (**2a/2b/2c**) was stirred for 2 h at -78 °C and used *in-situ* for future reactions.

4.2.2 LDA as a lithiating agent

A solution of **1a** (0.96 g, 4 mmol, 1.0 equiv)/ **1b** (0.94 g, 4 mmol, 1.0 equiv)/ **1c** (1.1 g, 4 mmol, 1.0 equiv) in dry THF (50 mL) was taken in a flame dried 3-necked 100 mL RBF. In another three-necked 100 mL RBF, n-BuLi (6.04 mL, 8 mmol, 1.39 N in hexane, 2.0 equiv) was added drop-wise to a solution of diisopropylamine (0.8 g, 1.1 mL, 8 mmol, 2.0 equiv) in THF (20 mL) at -10 °C to form lithium diisopropylamide (LDA). The temperature of the RBF containing **1a/1b/1c** was lowered to -78 °C and LDA was added slowly via cannula. The color of the suspension changed immediately to dark reddish brown indicating the

formation of the carbanion (**2a/2b/2c**). The solution containing **2a/2b/2c** was further stirred for 2 h at -78 °C and used *in-situ* for future reactions.

4.3 Treatment of 2a/2b/2c with elemental selenium

Selenium (0.63 g, 8 mmol) was added to the solution containing **2a/2b/2c** at -78 °C. The reaction mixture was slowly brought to the room temperature and stirred till the whole selenium was dissolved. Dissolution of selenium indicated the formation of the selenolate anion (**2a/2b/2c-Se**).

4.3.1 Bis(3-(4-chloro-N,N-diisopropylpyridine-2-carboxamide)) diselenide (3a)

The solution containing **2a-Se** was diluted with water and exposed to aerial oxidation for 30 min. The mixture was extracted with chloroform and the organic layer was dried over anhydrous sodium sulphate. Solvent was removed on a rota-evaporator and the residue was purified by column chromatography using silica gel and hexane ethyl acetate as eluent (10:3) to afford **3a** as yellow powder. Yield 0.83 g (65% n-BuLi), 0.89 g (70% LDA). m.p. 232-233 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm): 8.34-8.35 (d, *J* = 5.2 Hz, 2H), 7.34-7.35 (d, *J* = 5.2 Hz, 2H), 3.55-3.61 (m, 2H), 3.43-3.49 (m, 2H), 1.48-1.49 (d, *J* = 6.8 Hz, 12H), 1.03-1.04 (d, *J* = 6.6 Hz, 12H). ¹³C NMR (400 MHz, CDCl₃): δ (ppm): 165.4, 160.2, 150.7, 148.4, 123.9, 123.6, 50.0, 45.0, 19.6, 19.0. ⁷⁷Se NMR: δ (ppm): 444.2. IR (KBr, cm⁻¹): 3095, 2970, 1628, 1537, 1477, 1427, 1367, 1325, 1296, 1208, 1132, 1060, 850, 728, 616. MS (ESI): 639 [M⁺, ⁸⁰Se, ³⁶Cl]. Anal. Calcd (%) for C₂₄H₃₂Cl₂N₄O₂Se₂: C, 45.21, H, 5.02, N, 8.79. Found: C, 45.35, H, 5.30, N, 8.55.

4.3.2 Bis(3-(4-methoxy-N,N-diisopropylpyridine-2-carboxamide)) diselenide (3b)

Elemental selenium (0.63 g, 8 mmol, 2.0 equiv) was added to the solution containing **2b** at -78 °C. The temperature was slowly raised to room temperature for the complete dissolution of selenium. The resulting solution containing the selenolate anion (**2b-Se**) was hydrolyzed and worked up as described previously for **3a** (section 2.5.1). Yield: 0.76 g (61% n-BuLi), 0.85 g (68% LDA). ¹H NMR (400 MHz, CDCl₃): δ (ppm): 8.35-8.37 (d, *J* = 5.7 Hz, 2H), 6.75-6.77 (d, *J* = 5.7 Hz, 2H), 3.7 (s, 6H), 3.48-3.55 (m, 2H), 3.40-3.47 (m, 2H), 1.46-1.48 (d, *J* = 6.8 Hz, 12H), 1.01-1.03 (d, *J* = 6.6 Hz, 12H). ⁷⁷Se NMR: δ (ppm): 369.5. ¹³C NMR (400 MHz, CDCl₃): δ (ppm): 167.0, 166.7, 160.5, 150.6, 117.1, 106.1, 56.2, 50.8, 45.8, 20.6, 20.2. IR (KBr, cm⁻¹): 2924, 1710, 1624, 1364, 1218, 1089, 927, 770, 668, 530. MS (ESI): 631 [(M + H)⁺, ⁸⁰Se]. Anal. Calcd (%) for C₂₆H₃₈N₄O₄Se₂: C, 49.69, H, 6.09, N, 8.91. Found: C, 49.76, H, 6.03, N, 8.49.

4.3.3 Bis(3-(4-butoxy-N,N-diisopropylpyridine-2-carboxamide)) diselenide (3c)

Elemental selenium (0.63 g, 8 mmol, 2.0 equiv) was added to the solution containing **2c** at -78 °C. The temperature was slowly raised to room temperature for the complete dissolution of selenium. The resulting solution containing the selenolate anion (**2c-Se**) was hydrolyzed and worked up as described previously for **3a** (section 2.5.1). Yield: 0.76 g (61% n-BuLi), 0.85 g (68% LDA). m.p. 198-200 °C. ¹H NMR (400 MHz, CDCl₃): δ (ppm): 8.33-8.35 (d, *J* = 5.8 Hz, 2H), 6.76-6.78 (d, *J* = 5.8 Hz, 2H), 4.01-4.04 (t, 4H), 3.52-3.55 (m, 2H), 3.41-3.44 (m, 2H), 1.62-1.67 (m, 4H), 1.48-1.57 (m, 4H), 1.45-1.46 (d, *J* = 6.8 Hz, 12H), 0.99-1.01 (d, *J* = 6.6 Hz, 12H),

0.93-0.96 (t, 6H). ⁷⁷Se NMR: δ (ppm): 366.0. MS (ESI): 715 [(M+H)⁺, ⁸⁰Se].

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