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Synthesis and characterization of chalcogen (S and Se) derivatives of 4-chloro- and 4-methoxy-*N*,*N*-diisopropylpyridine-2-carboxamide: X-ray structure of 4-methoxy-3-(sulfanylmethyl)- and 4-chloro-3-(selenenylbenzyl)-*N*,*N*-diisopropylpyridine-2-carboxamide

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ABSTRACT

Synthesis of chalcogen (S and Se) derivatives of 4-chloro- and 4-methoxy-*N*,*N*-diisopropylpyridine-2-carboxamide (**1a** and **1b** respectively) has been reported. **1a** and **1b** were lithiated with 2 equiv. of *n*-BuLi or LDA at −78 °C. Addition of elemental sulfur or selenium to the carbanion led to the formation of corresponding thiolate or selenolate anions respectively. The selenolate anions were aerial oxidized to afford the corresponding diselenides. The thiolate/selenolate anions were quenched with a variety of electrophiles to give unsymmetrical thio/selenoalkanes in moderate to good yields. Reductive cleavage of Se—Se bond has also been studied. The synthesized compounds were characterized by elemental analysis, NMR (^{1}H, ^{13}C and ^{77}Se), FT-IR and mass spectral techniques. Crystal structures of two compounds, **6b** and **7a**, were determined by single crystal X-ray crystallography. Their crystal structure exhibits 1,4-type S···OCH_3 and Se···Cl intramolecular secondary interactions respectively. The relative thermal stability of **3a**, **3b** and **4a** has also been established by thermogravimetric analysis.

1. Introduction

Interest in the field of organochalcogens having E—X (E = S or Se; X = halogen, O or N) intramolecular secondary interactions stems from their utility in organic synthesis [1,2], biochemistry [3–5] and material science [6,7]. These secondary interactions are known to increase the stability of many organochalcogen compounds [8,9]. Compared to organoseleniums, their sulfur congeners are more stable. However, compounds having Se—X secondary interactions are found to be equally or in some cases even more stable than the organosulfur compounds devoid of these interactions [10]. Internally stabilized organoseleniums have shown much better antioxidant properties, as they form stable intermediates during the process involving the removal of oxidants [11]. The metal chalcogenolates containing these moieties also serve as excellent single source precursors of the semiconducting materials [12,13]. In addition to these, the organoselenium compounds containing the pyridyl moieties serves as an efficient reagents in the selenoxide elimination reactions for the synthesis of terminal olefins [14].

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. This is probably due to the lack of efficient methodology for their synthesis. In this paper, we report an efficient and convenient synthesis of various hitherto unknown internally chelated organosulfur and -selenium compounds derived from 4-chloro- and 4-methoxy-*N*,*N*-diisopropylpyridine-2-carboxamide (**1a** and **1b** respectively). Reductive cleavage of Se—Se bond with lithium aluminum hydride and sodium borohydride has also been studied. Single crystal X-ray studies of 4-methoxy-3-(sulfanylmethyl)- and 4-chloro-3-(selenenylbenzyl)-*N*,*N*-diisopropylpyridine-2-carboxamide (**6a** and **7b** respectively) along with thermogravimetric analysis of **3a**, **3b** and **4a** have also been described.

2. Results and discussion

2.1. Preparation of diselenide derivatives of *1a* and *1b*

Reaction of **1a** or **1b** with 2 equiv. of *n*-BuLi in dry THF at −78 °C affected lithiation at the β-position of the pyridine ring, resulting in the formation of reddish brown solution of the carbanion. Insertion of elemental selenium to the carbanion led to the formation of

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corresponding selenolate anion. The selenolate anion, upon hydrolysis and subsequent aerial oxidation offered the corresponding diselenide **3a** and **3b** respectively in good yields (Scheme 1). Both these compounds are high melting solids and are highly stable at elevated temperatures (upto 260 °C).

2.2. Preparation of unsymmetrical 3-sulfanyl- and 3-selenenylalkyl derivatives of *1a* and *1b*

The thiolate/selenolate anions, formed by insertion of elemental sulfur/selenium to the carbanion, were reacted with a variety of electrophiles (Table 1) at −78 °C, and then hydrolyzed at room temperature to give 3-sulfanyl- and 3-selenenylalkyl derivatives of **1a** and **1b** in moderate to good yields (Scheme 1, Table 1). Further, in an effort to synthesize bis(selenenyl) ethane, we reacted the selenolate anion of **1a** with 1,2-dibromoethane. However to our surprise, 4-chloro-(3-selenenylethylbromide)-*N*,*N*-diisopropylpyridine-2-carboxamide (**8a**) was the only product formed. This suggests toward the substitution of one of the two bromo group with the selenolate (R–Se^-) anion.

In another variation for the synthesis of unsymmetrical derivatives, the carbanion was directly reacted with dibenzyl diselenide to give the compound **8a** in 41% yield. The performance of *n*-BuLi *vis-a-vis* LDA was also tested in the above reactions. It was found that the yields obtained with LDA were 15–20% more than that obtained with *n*-BuLi. Increasing the amount of LDA form 2 to 3 equiv. neither led to the formation of any dilithiated product nor showed any substantial increase in the yield of the reaction.

2.3. Reductive cleavage of Se–Se bond in *3a*

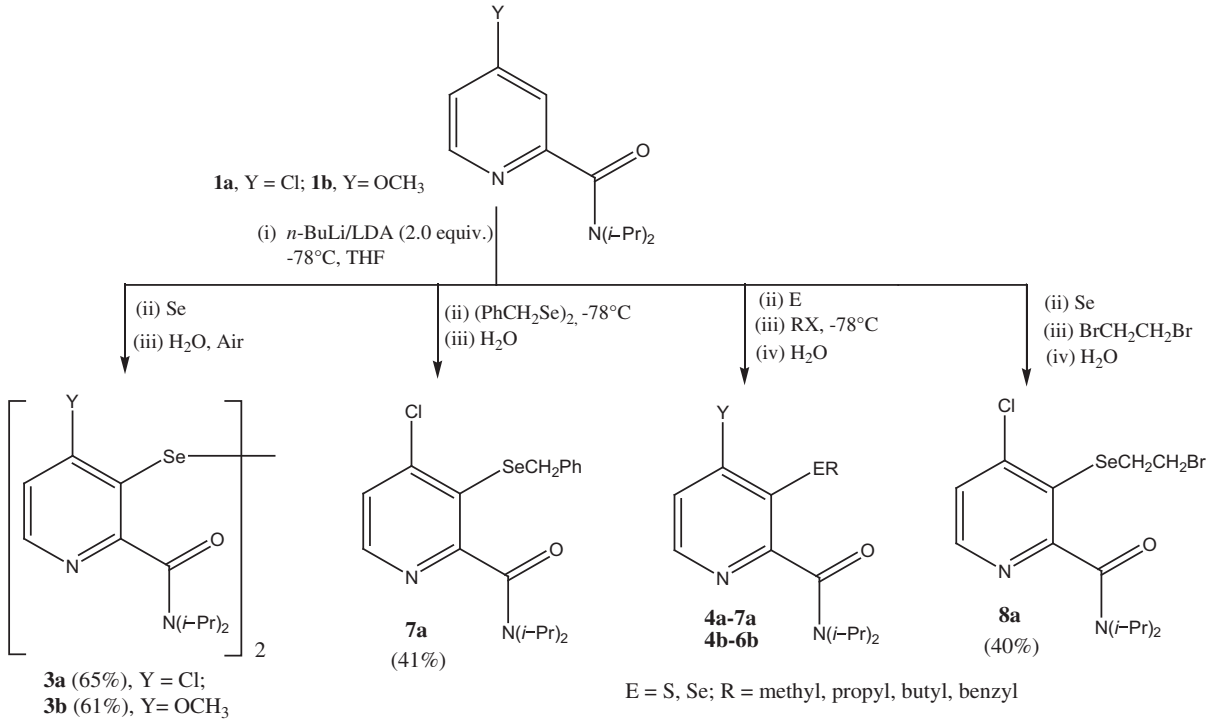
Reducing agents like lithium aluminum hydride is known to cleave Se–Se bond in various diorgano diselenides. However, it has the potential to reduce the carboxamide functional group to the corresponding amines, aldehydes or alcohols. In light of these findings, we decided to study the reductive cleavage Se–Se bond in **3a** as a representative example. Addition of $LiAlH_4$ powder to a solution of **3a** in dry THF immediately led to the change in the color of the solution from dark orange to pale yellow with evolution of hydrogen gas. Addition of iodomethane to this solution afforded **5a** in moderate yield. No product due to the action of $LiAlH_4$ on the carboxamide function was noticed in this reaction. Thus it can be concluded that $LiAlH_4$ chemoselectively cleaves Se–Se bond without disturbing the carboxamide group in these compounds. The use of $NaBH_4$ in ethanol instead of $LiAlH_4$ also led to an efficient cleavage of Se–Se bond. The selenolate anion thus formed gave **5a** in near quantitative yield on quenching with iodomethane at 40 °C (Scheme 2).

Table 1
Preparation of unsymmetrical thio- and selenoalkyl derivatives of **1a** and **1b**.

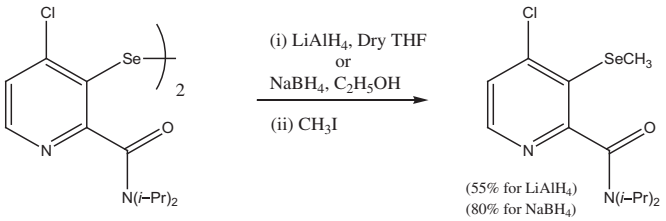
Entry	Compound	Y	Reagent	R	X	E	Yield %
1	**4a**	Cl	*n*-BuLi	$-CH_2-CH_2-CH_3$	Br	S	64
2	**4b**	OCH_3	*n*-BuLi	$-CH_2-CH_2-CH_3$	Br	Se	60
3	**5a**	Cl	*n*-BuLi	$-CH_3$	I	Se	61
4	**5a**	Cl	LDA	$-CH_3$	I	Se	82
5	**5b**	OCH_3	*n*-BuLi	$-CH_3$	I	Se	64
6	**5b**	OCH_3	LDA	$-CH_3$	I	Se	78
7	**6a**	Cl	*n*-BuLi	$-C_4H_9$	I	Se	57
8	**6b**	OCH_3	LDA	$-CH_3$	I	S	74
9	**7a**	Cl	*n*-BuLi	$-CH_2C_6H_5$	Cl	Se	59
10	**8a**	Cl	*n*-BuLi	$-CH_2-CH_2Br$	Br	Se	40

2.4. Spectroscopic studies

The synthesized compounds were characterized by elemental analysis, NMR (^1H ^{13}C and ^{77}Se), FT-IR and mass spectral techniques. Compared to the parent compound (**1a** and **1b**), IR spectra of the compounds, **3a**–**8a** and **3b**–**6b**, did not show any significant change in the carbonyl stretching frequencies (υCO, 1624–1636 cm^{-1}). Interestingly, The peak corresponding to the υCO for **5b** and **6b** appears almost at the same frequency. This indicates that the change



Scheme 1. Preparation of symmetrical diselenides and unsymmetrical 3-sulfanyl- and 3-selenenylalkyl derivatives of **1a** and **1b**.



Scheme 2. Reductive cleavage of Se–Se bond with $LiAlH_4$ or $NaBH_4$.

in the chalcogen atom has no effect on the carbonyl stretching frequencies of these compounds. The ^1H NMR spectra of these compounds shows two singlets in the aromatic region indicating deprotonation of the parent compound. The spectra contains two multiplets due to two non-equivalent $-\mathbf{CH}(CH_3)_2$ groups and two doublets corresponding to two non-equivalent isopropyl methyl groups. Also, in the ^{13}C NMR spectra there are two signals for the methyne carbons and two signals for the methyl carbons. 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. There is no substantial change in the ^{13}C chemical shift of the carbonyl carbons in these compounds. In conclusion, both the IR and the NMR data suggests toward the absence of E···O (carbonyl) interactions. ^{77}Se NMR of the compound **5a**, **5b** and **7a** were recorded with diphenyl diselenide as the external standard. Change in the substituent around selenium atom results in large change in the magnitude of chemical shift in its spectra. The selenium signal in the spectrum of **5a** appears downfield at 162.04 (δ ppm) when compared to **5b** (93.79, δ ppm), whereas, the signal in **7a** appears further downfield at 302.38 δ (ppm). The ES mass spectra of organoselenium compounds gave distinct molecular ion peaks with characteristic isotopic patterns. In addition to the molecular ion peak, the mass spectrum of **3b** exhibits a peak corresponding to R–Se–$(Se)_6$–Se–R species at m/z 943. However, no product corresponding to this polyselenide species was isolated from the reaction mixture. The mass spectrum of all the unsymmetrical chalcogenides (**4a**–**8a**, **4b**–**6b**) not only showed a signal corresponding to the molecular ion peak but also exhibited a peak at double the m/z value of the molecular ion peak. In this case also no such species was found in any of the reaction products. Therefore, it appears that formation of the polyselenide species occurs only under the mass spectroscopic conditions.

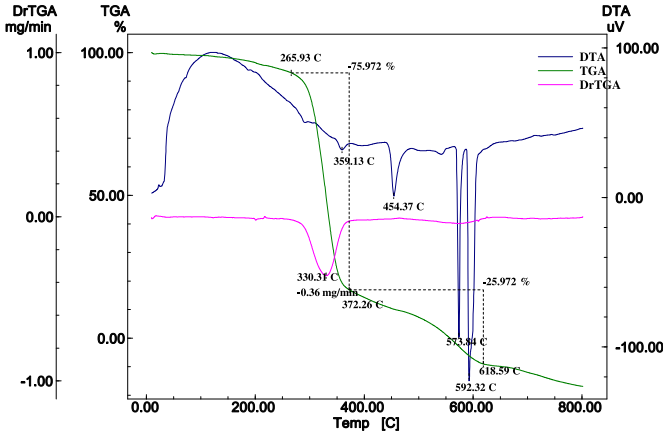


Fig. 2. TGA, DTA and Dr. TGA curves of **3b**.

2.5. Thermogravimetric studies

Thermal stability of **3a** is clearly depicted from the TG/DTA curves shown in Fig. 1. The compound **3a** is thermally stable upto 256 °C and then decomposes in three stages. A large reaction interval of 341 °C suggests that this compound decomposes very slowly. DTG shows two peak maxima at 293 °C and 382 °C as the maximum rate of decomposition. The compound **3b** is thermally stable upto 266 °C (Fig. 2). After this temperature it undergoes decomposition in two stages. No residue was left in the pan after the full scan. This suggests that volatile selenium containing intermediates are formed during the decomposition process. Reaction interval of 353 °C is slightly higher that of **3a**.

In order to compare the thermal stability of unsymmetrical selenides, we investigated the thermal behavior of **4b**. The

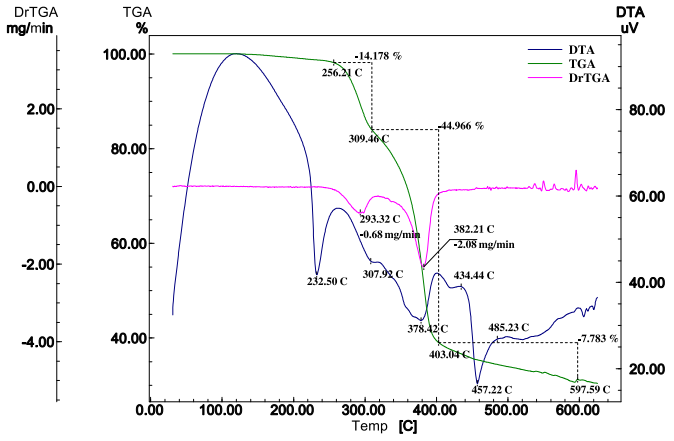


Fig. 1. TGA, DTA and Dr. TGA curves of **3a**.

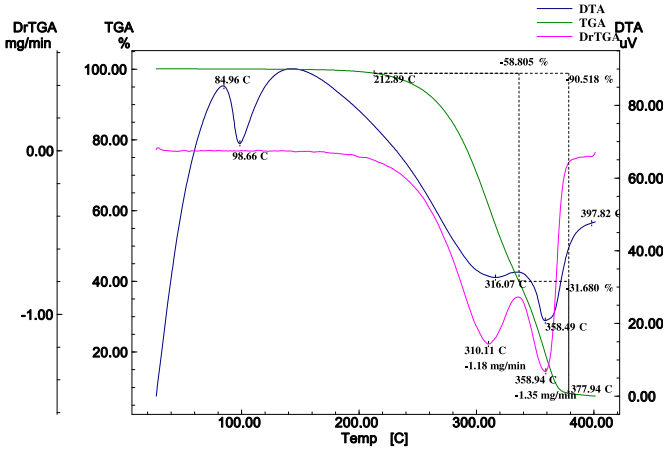


Fig. 3. TGA, DTA and Dr. TGA curves of **4a**.

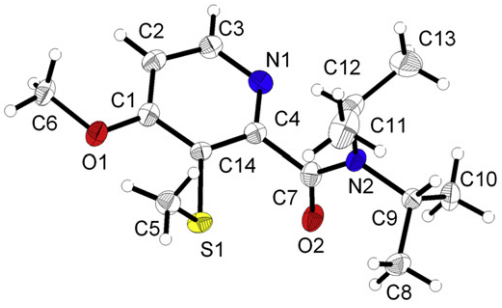


Fig. 4. Molecular structure of **6b** with atom numbering scheme.

compound **4b** is thermally stable upto 212 °C after which it decomposes in two steps (Fig. 3) leaving behind 9.52% residue, which is less than the expected percentage of selenium (22.3%) present in the sample. DTG curve confirmed the two step decomposition, showing maximum rates of decomposition at 310 °C and 359 °C. Reaction interval of 165 °C suggests that the decomposition is faster than **3a** and **3b**. From above discussion it is clear that the thermal stability of these compounds is in the following order: **3b** > **3a** > **4b**

2.6. Solid state structural features of *6b* and *7a*

Fig. 4 shows the molecular geometry and the crystallographic numbering scheme of **6b**. Selected bond lengths and angles are listed in Table 2. The molecule crystallizes in orthorhombic *P*bca space group with cell parameters ($a = 14.730(5)$ Å, $b = 13.396(5)$ Å, $c = 15.065(5)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$).

An interesting aspect in the structure of **6b** is the presence of intramolecular secondary 1,4-type S···OCH_3 interaction. The S(1)–O(1) atomic distance is 2.992 Å, which is significantly shorter than the sum of their van der Waals radii of 3.32 Å. Short intramolecular contacts are also observed between O(2)–H(8C) and O(2)–H(10B) (Table 3). No interaction is observed between sulfur and the carbonyl oxygen as oxygen atom points away from the sulfur center. Short intermolecular distances between O(2)–H(5A), O(2)–C(5), H(5C)–H(13C) and C(5)–H(13C) (Table 4) are also observed in the crystal structure. The S–Me unit is oriented out of the plane of the pyridine ring [torsion angle C(1)–C(14)–S(1)–C(5) of −53.2°] mainly due to the steric effects of the *ortho* groups. The geometry around the sulfur is 'V' shaped with a C(14)–S(1)–C(5) angle of 104.03 (19)° and the geometry around C(9) and C(12) is distorted tetrahedral due steric overcrowding. The C(Sp^2)–S bond length [1.777 (4) Å] is slightly shorter than that found in 5,5′-dibromo-2,2′-dipryidyl disulfide (1.782 Å) [15] and the C(Sp^3)–S bond length [1.787 (4) Å] is significantly shorter than that found in other organosulfur compounds having C(Sp^3)–S bond [16,17].

Table 3
The shorter intramolecular distances (Å) in **6b** and **7a** () [a].

Atoms in **6b**	Distance	Atoms in **7a**	Distance
S(1)–O(1)	2.992 (3.32)	Se (1)–Cl(1)	3.345 (3.65)
O(1)–H(5B)	2.328 (2.72)	O(1)–C(19)	3.045 (3.22)
O(2)–H(8C)	2.483 (2.72)	O(1)–C(19)	3.028 (3.22)
O(2)–H(10B)	2.524 (2.72)	O(1)–C(17)	2.814 (3.22)
–	–	O(1)–H(19C)	2.481 (2.72)

[a] Values in the parenthesis is the sum of the van der Waals radii.

Selected bond length and angles of **7a** are given in Table 2 and its molecular structures with atom numbering scheme is shown in Fig. 5a. The molecule crystallizes in tetragonal *P*-42(1)c space group with cell parameters ($a = 21.517(2)$ Å, $b = 21.517(2)$ Å, $c = 8.2988(13)$ Å, $\alpha = 90°$, $\beta = 90°$, $\gamma = 90°$,). The coordination geometry around Se is V-shaped with bond angle C(8)–Se(1)–C(7) of 98.01(18)°. Intramolecular secondary 1,4-type Se(1)–Cl(1) interaction was noticed in this compound (Fig. 5b, Table 3). The 1,4-type chalcogen–heteroatom secondary interactions are very rare and greatly influence the structural features of the compounds [18,19]. Similar to **6b**, no Se–O(carbonyl) secondary interaction was noticed. The dihedral angle between the planes containing the amide group and pyridine ring are orthogonal to each other with C–O(carbonyl) bond pointing away from the selenium center. This is the reason behind the absence of any 1,5-Se–O(carbonyl) intramolecular interactions. This observation is reflected in very small change in its carbonyl stretching frequency with respect to the parent compound (**1a**). It has been found that the compounds showing 1,5-Se–O(carbonyl) interactions have selenium and oxygen atoms in the same plane [20]. The compounds which don't have Se–O secondary interactions have both these atoms in different planes [21]. The crystal packing diagram of **7a** (Fig. 6) shows short intermolecular distances between atoms listed in Table 4. Weak intermolecular C(3)–H(3)–Se (C–H–Se angle of 126°) and C(3)–H(3)–H(16A) interactions results in a V-shaped geometry around the H(3) with an angle H(16A)–H(3)–Se(1) of 72.69°. The rare C–H–Se intermolecular secondary interactions have been reported in compounds with C–H–Se angle of 129° [22]. The C(Sp^3)–Se bond length is longer and the C(Sp^2)–Se bond length is comparable to that found in tris(2-pyridylseleno) methane [23]. The selenium atom is planar with the pyridine ring whereas, it is orthogonal to the benzyl ring. The bond angles and bond length of the pyridine ring is comparable to that in dipyridyl diselenide [24].

Table 2
Bond lengths [Å] and angles [°] for **6b** and **7a**.

Compound 6b					
N(2)–C(7)	1.348(5)	N(2)–C(12)	1.468(6)	O(2)–C(7)	1.229(5)
O(1)–C(1)	1.337(5)	O(1)–C(6)	1.446(5)	C(14)–S(1)	1.777(4)
C(9)–C(8)	1.512(6)	C(4)–C(7)	1.519(6)	S(1)–C(5)	1.787(5)
C(7)–N(2)–C(12)	122.3(4)	C(12)–N(2)–C(9)	116.8(3)	C(4)–C(14)–S(1)	118.9(3)
N(2)–C(9)–C(8)	112.5(3)	C(8)–C(9)–C(10)	112.3(4)	C(14)–C(4)–C(7)	120.1(4)
O(2)–C(7)–N(2)	124.7(4)	C(11)–C(12)–C(13)	112.5(5)	N(2)–C(12)–H(001)	102(3)
C(11)–C(12)–H(001)	110(4)	C(9)–C(8)–H(8A)	109.5	C(14)–S(1)–C(5)	104.03(19)
Compound 7a					
C(1)–C(7)	1.501(6)	C(7)–Se(1)	1.974(4)	C(8)–Se(1)	1.924(4)
C(9)–Cl(1)	1.723(4)	C(12)–C(13)	1.517(5)	C(13)–O(1)	1.232(5)
C(13)–N(2)	1.338(5)	C(14)–N(2)	1.465(5)	C(14)–C(16)	1.527(7)
C(1)–C(7)–Se(1)	111.2(3)	C(9)–C(8)–Se(1)	122.8(3)	N(1)–C(12)–C(13)	114.7(3)
C(8)–C(12)–C(13)	120.0(4)	O(1)–C(13)–N(2)	124.5(4)	O(1)–C(13)–C(12)	116.7(4)
N(2)–C(14)–C(16)	112.7(4)	C(16)–C(14)–C(15)	112.4(4)	C(13)–N(2)–C(17)	120.7(4)
C(14)–N(2)–C(17)	116.8(4)	C(8)–Se(1)–C(7)	98.01(18)		

Table 4
The shorter intermolecular distances (Å) in **6b** and **7a** ()[a].

Atoms in **6b**	Distance	Atoms in **7a**	Distance
O(2)–H(5A)	2.365 (2.72)	Se (1)–H(3)	3.031 (3.1)
O(2)–C(5)	3.203 (3.22)	H(16A)–H(3)	2.358 (2.4)
H(5C)–H(13C)	2.365 (2.4)	H(14)–C(15)	2.830 (2.9)
C(5)–H(13C)	2.886 (2.9)	O(1)–H(10)	2.561 (2.72)
–	–	N(1)–H(11)	2.730 (1.75)
–	–	H(7B)–C(2)	2.782 (2.9)
–	–	H(7B)–C(3)	2.825 (2.9)

[a] Values in the parenthesis is the sum of the van der Waals radii.

3. Conclusion

Synthesis of organochalcogen (S, Se) compounds derived from **1a** and **1b** has been achieved by a method involving lithiation of **1a** and **1b** 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 IR and ^{13}C NMR spectra of the prepared compounds indicates toward the absence of E–O (carbonyl) interactions. The single crystal X-ray structures of **6b** and **7a** substantiate the above facts, and establishes the presence of 1,4-type S···O–CH_3 and Se···Cl intramolecular secondary interactions.

4. Experimental

4.1. General

All experiments were carried out in dry oxygen free nitrogen atmosphere. Infrared spectra were recorded between KBr pellets on a Perkin–Elmer Model 1430. ^1H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ using TMS as internal standard on Bruker AC, 400 MHz spectrometer. ^{77}Se NMR spectra were recorded in $CDCl_3$ using diphenyl diselenide as external standard on Bruker AMX500 spectrometer. The ESI mass spectra were taken on Water Q-TOF Micro spectrometer. The elemental analysis was carried out by using Elementar VarioMICRO analyzer. The thermogravimetric analysis was done on Shimadzu DTG 60H (simultaneous TG/DTA module). The samples were loaded on an Alumina crucible and heated under nitrogen at the rate of 20 °C/min. Compound **1a** and **1b** was prepared by literature method [25].

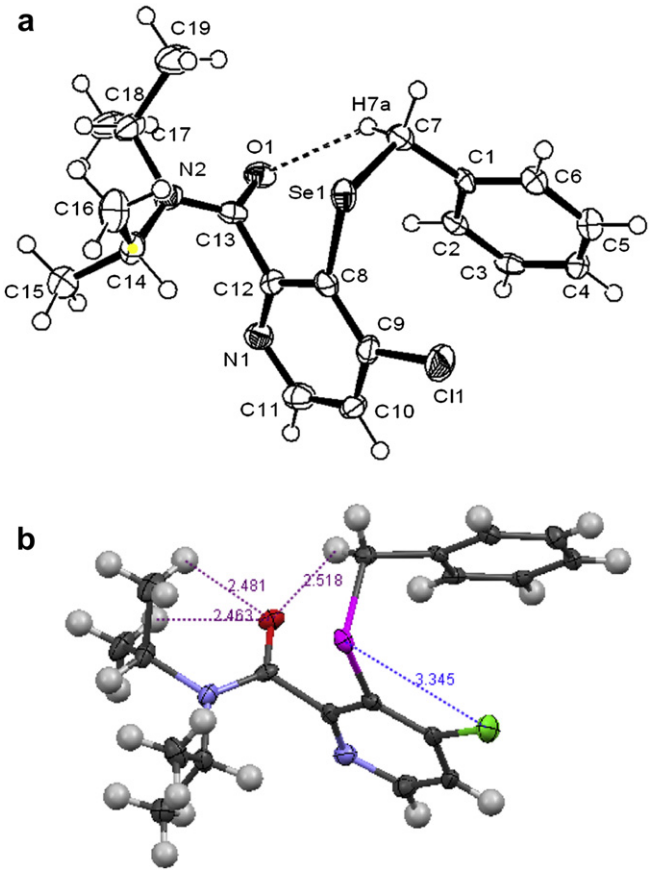


Fig. 5. a: Molecular structure of **7a** with atom numbering scheme. b: Molecular structure of **7a** exhibiting intramolecular non-bonded interactions.

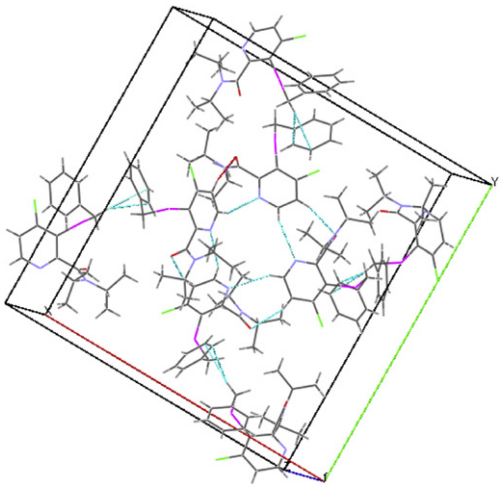


Fig. 6. Crystal packing of **7a**.

4.2. General method for the preparation of chalcogenolate anion of *1a* and *1b*

To a vigorously stirred solution of **1a** (0.962 g, 4 mmol) or **1b** (0.90 g, 4 mmol) in dry THF at −78 °C, *n*-BuLi (1.39 N in hexane, 6.0 ml, 8 mmol) was added drop-wise. The reaction mixture was stirred for 2 h at the same temperature. To the dark red solution of the carbanion, elemental selenium (0.632 g, 8 mmol) or sulfur (0.257 g, 8 mmol) was added and the reaction mixture was slowly brought to the room temperature. After the complete dissolution of elemental chalcogen the reaction was subjected to conditions described below.

4.2.1. Bis[3-(4-chloro-N,N-diisopropylpyridine-2-carboxamide)] diselenide (*3a*)

The selenolate anion of **1a** formed as above was hydrolyzed at room temperature by adding 20 ml of water. The reaction mixture was subjected to aerial oxidation for 30 min. The organic layer was extracted with diethyl ether (3 × 50 ml) and dried over anhydrous sodium sulfate. The solvent was removed on a rota-evaporator and the crude residue was purified by column chromatography using silica gel (60–120 mesh) and using hexane–ethyl acetate as eluent (5:4). Yield 0.83 g (65%), m.p. 232–233 °C, ^1H NMR: $CDCl_3$, 400 MHz 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, J = 6.6 Hz, 2H), 3.43–3.49 (m, J = 6.8 Hz, 2H), 1.48–1.49 (d, J = 6.8 Hz, 12H,), 1.03–1.04 (d, J = 6.6 Hz, 12H). ^{13}C NMR: $CDCl_3$, 400 MHz δ (ppm): 165.4, 160.2, 150.7, 148.4, 123.9, 123.6, 50.0, m 45.0, 19.6, 19.0. IR (KBr, cm^{-1}): 2970, 1628, 1537, 1477, 1427, 1367, 1325, 1296, 1208, 1132, 1060, 850, 728, 616. MS (ESI): 639 [$M^{+\$\,80}Se$]. *Anal. Calcd* (%) for $C_{24}H_{32}Cl_2N_4O_2Se_2$: C, 45.21, H, 5.02, N, 8.79. Found: C, 45.35, H, 5.30, N, 8.55.

4.2.2. Bis[3-(4-methoxy-N,N-diisopropylpyridine-2-carboxamide)] diselenide (**3b**)

The selenolate anion of **1b** was hydrolyzed and subjected to aerial oxidation for 30 min. The reaction mixture was worked-up as described above. Yield: 0.76 g (61%), ^{1}H NMR: $CDCl_3$, 400 MHz 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, J = 6.6 Hz, 2H), 3.40–3.47 (m, J = 6.8 Hz, 2H), 1.46–1.48 (d, J = 6.8 Hz, 12H,), 1.01–1.03 (d, J = 6.6 Hz, 12H). IR (KBr, cm^{-1}): 2924, 1710, 1624, 1364, 1218, 1089, 927, 770, 668, 530. MS (ESI): 631 $[M + H]^+$ 630 $[M^{+\$}\ ^{80}Se]$, 629 $[M - H]^+$. *Anal. Calcd* (%) for $C_{26}H_{38}N_4O_4Se_2$: C, 49.69, H, 6.09, N, 8.91. Found: C, 49.76, H, 6.03, N, 8.49.

4.3. General method for the preparation of unsymmetrical 3-sulfanyl- and 3-selenenylalkyl derivatives of **1a** and **1b**

The chalcogenolate anion of **1a**/**1b** was cooled to −78 °C and the desired electrophile (8 mmol) was added drop-wise. The reaction mixture was slowly brought to room temperature and stirred for 30 min. The nitrogen supply to the reaction mixture was stopped. The reaction mixture was hydrolyzed and extracted with diethyl ether (3 × 50 ml). The organic layer was dried over anhydrous sodium sulfate. The solvent was removed on a rota-evaporator and the crude residue was purified by column chromatography using silica gel and hexane-ethyl acetate as eluent (10:3).

4.3.1. 4-Chloro-3-(sulfanylpropyl)-N,N-diisopropylpyridine-2-carboxamide (**4a**)

Electrophile: 1-Bromopropane (0.984 g, 0.73 ml, 8 mmol). Yield: 0.8 g (64%), m.p. 68–70 °C, ^{1}H NMR: $CDCl_3$, 400 MHz δ (ppm): 8.32–8.33 (d, J = 5.2 Hz, 1H), 7.28–7.29 (d, J = 5.2 Hz, 1H), 3.44–3.51 (m, J = 6.8 Hz, 1H), 3.28–3.34 (m, J = 6.6 Hz, 1H), 2.86–2.90 (m, 2H), 1.52–1.53 (d, J = 6.7 Hz, 6H,), 1.32–1.37 (m, 2H), 1.05–1.12 (broad doublet, 6H), 0.81–0.85 (t, J = 7.3 Hz, 3H). ^{13}C NMR: $CDCl_3$, 400 MHz δ (ppm): 166.3, 162.0, 151.2, 149.3, 127.6, 124.4, 51.0, 45.9, 38.3, 36.1, 31.4, 22.9, 21.8, 20.5, 13.6. IR (KBr, cm^{-1}): 2929, 2435, 2132, 1716, 1636, 1439, 1364, 1218, 1090, 771, 670, 530. MS (ESI): 314 $[M^{+\$}]$. *Anal. Calcd* (%) for $C_{15}H_{23}ClN_2OS$: C, 57.22, H, 7.36, N, 8.90, S, 10.18. Found: C, 57.52, H, 7.33, N, 8.11, S, 9.31.

4.3.2. 4-Methoxy-3-(selenenylpropyl)-N,N-diisopropylpyridine-2-carboxamide (**4b**)

Electrophile: 1-Bromopropane (0.984 g, 0.73 ml, 8 mmol). Yield: 0.86 g (60%), m.p. 46–48 °C, ^{1}H NMR: $CDCl_3$, 400 MHz δ (ppm): 8.39–8.40 (d, J = 5.6 Hz, 1H), 6.73–6.75 (d, J = 5.7 Hz, 1H), 3.95 (s, 3H), 3.44–3.56 (m, J = 6.8, 6.2, 6.7 Hz, 2H), 2.86–2.91 (t, J = 7.3, 7.4 Hz, 2H), 1.66.1.69 (m, 2H), 1.56–1.65 (d, J = 8.0 Hz, 6H), 1.15–1.17 (d, J = 6.6 Hz, 6H), 0.95–0.98 (t, J = 7.3, 7.4 Hz, 3H). ^{13}C NMR: $CDCl_3$, 400 MHz δ (ppm): 167.1, 167.0, 161.0, 150.3, 111.2, 105.8, 99.9, 56.2, 50.9, 45.9, 32.2, 23.6, 20.6, 14.4, 1.02. IR (KBr, cm^{-1}): 2966, 1625, 1566, 1468, 1427, 1371, 1335, 1296, 1212, 1132, 1039, 817, 751, 616. MS (ESI): 359 $[M + H]^+$. *Anal. Calcd* (%) for $C_{16}H_{26}N_2O_2Se$: C, 53.78, H, 7.33, N, 7.84. Found: C, 53.69, H, 7.22, N, 7.58.

4.3.3. 4-Chloro-3-(selenenylmethyl)-N,N-diisopropylpyridine-2-carboxamide (**5a**)

Electrophile: Iodomethane (1.14 g, 0.5 ml, 8 mmol). Yield: 0.81 g (61%, *n*-BuLi), 1.1 g (82%, LDA) m.p. 82–84 °C, ^{1}H NMR: $CDCl_3$, 400 MHz δ (ppm): 8.39–8.41 (d, J = 5.3 Hz, 1H), 7.36–7.37 (d, J = 5.2 Hz, 1H), 3.52–3.59 (m, J = 6.9 Hz, 1H), 3.3–3.42 (m, J = 6.7 Hz, 1H), 2.3 (s, 3H), 1.59–1.69 (d, J = 6.9 Hz, 6H,), 1.18–1.20 (d, 6.6 Hz, 6H), 0.9 (t, 3H). ^{13}C NMR: $CDCl_3$, 400 MHz δ (ppm): 166.9, 161.9, 151.1, 149.3, 124.3, 123.4, 51.0, 46.0, 20.5, 20.1, 9.6. ^{77}Se NMR: δ (ppm): 162.04. IR (KBr, cm^{-1}): 2968, 2361, 1629, 1547, 1466, 1422, 1370, 1331, 1209, 1162, 1098, 916, 824, 733, 634, 605, 532, 495. MS (ESI): 335 $[M^{+\$}, {}^{80}Se, {}^{36}Cl]$, *Anal. Calcd* (%) for $C_{13}H_{19}ClN_2OSe$: C, 46.80, H, 5.74, N, 8.39. Found: C, 46.83, H, 5.88, N, 8.23.

4.3.4. 4-Methoxy-3-(selenenylmethyl)-N,N-diisopropylpyridine-2-carboxamide (**5b**)

Electrophile: Iodomethane (1.14 g, 0.5 ml, 8 mmol). Yield: 0.84 g (64%, *n*-BuLi), 1.02 g (78%, LDA), m.p. 140–142 °C, ^{1}H NMR: $CDCl_3$, 400 MHz δ (ppm): 8.47–8.48 (d, J = 4.8 Hz, 1H), 6.91–6.92 (d, J = 4.8 Hz, 1H), 4.0 (s, 3H), 3.55–3.58 (m, 1H), 3.43–3.46 (m, 1H), 2.3 (s, 3H), 1.60–1.62 (d, J = 6.8 Hz, 6H), 1.22–1.24 (d, J = 6.6 Hz, 6H). ^{13}C NMR: $CDCl_3$, 400 MHz δ (ppm): 167.0, 166.7, 160.5, 150.6, 117.1, 106.1, 56.2, 50.8, 45.8, 20.6, 20.2, 18.1. ^{77}Se NMR: δ (ppm): 93.79. IR (KBr, cm^{-1}): 3018, 2922, 2848, 1628, 1565, 1432, 1364, 1218, 1163, 1034, 770, 668, 530. MS (ESI): 329 $[(M - H)^+, {}^{80}Se]$, 330, $[M^{+\$}, {}^{80}Se]$, 331 $[(M + H)^+, {}^{80}Se]$. *Anal. Calcd* (%) for $C_{14}H_{22}N_2O_2Se$: C, 51.07, H, 6.73, N, 8.51. Found: C, 50.96, H, 6.89, N, 8.47.

4.3.5. 4-Chloro-3-(selenenylbutyl)-N,N-diisopropylpyridine-2-carboxamide (**6a**)

Electrophile: 1-Iodobutane (1.472 g, 0.91 ml, 8 mmol). Yield: 0.85 g (57%), m.p. low melting point solid. ^{1}H NMR: $CDCl_3$, 400 MHz δ (ppm): 8.31–8.32 (d, J = 5.3 Hz, 1H), 7.28.7.27 (d, J = 5.3 Hz, 1H), 3.44–3.50 (m, J = 6.8 Hz, 1H), 3.32–3.38 (m, J = 6.7 Hz, 1H), 2.9 (s, broad peak, 2H), 1.54–1.61 (m, J = 7.2–7.6 Hz, 2H,), 1.51–1.53 (d, J = 6.8 Hz, 6H), 1.31–1.36 (m, 7.3–7.6 Hz, 2H), 1.10 (s, broad peak, 6H), 0.80–0.84 (t, J = 7.4 Hz, 3H). ^{13}C NMR: $CDCl_3$, 400 MHz δ (ppm): 167.1, 162.8, 151.2, 149.6, 124.1, 122.6, 50.9, 45.9, 32.1, 30.1, 22.8, 20.5, 13.5. IR (KBr, cm^{-1}): 2970, 1643, 1537, 1469, 1368, 1258, 1211, 1136, 1040, 830, 728, 634, 604, 531. MS (ESI): 377, $[M^{+\$}, {}^{80}Se, {}^{36}Cl]$. *Anal. Calcd* (%) for $C_{16}H_{25}ClN_2OSe$: C, 51.15, H, 6.71, N, 7.45. Found: C, 51.47, H, 6.71, N, 7.29.

4.3.6. 4-Methoxy-3-(sulfanylmethyl)-N,N-diisopropylpyridine-2-carboxamide (**6b**)

Electrophile: Iodomethane (1.14 g, 0.5 ml, 8 mmol). Yield: 0.83 g, (74%), m.p. 142–143 °C, ^{1}H NMR: $CDCl_3$, 400 MHz δ (ppm): 8.32–8.33 (d, J = 5.8 Hz, 1H), 6.71–6.73 (d, 5.8 Hz, 1H), 3.90 (s, 3H), 3.44–3.48 (m, 1H), 3.37–3.40 (m, 1H), 2.29 (s, 3H), 1.51–1.53 (d, J = 6.8 Hz, 6H), 1.08–1.09 (d, 6H). ^{13}C NMR: $CDCl_3$, 400 MHz δ (ppm): 167.5, 166.5, 160.7, 150.6, 111.7, 105.9, 56.2, 50.9, 45.9, 29.7, 20.6, 20.2, 8.3. IR (KBr, cm^{-1}): 2922, 2435, 1629, 1560, 1458, 1364, 1338, 1217, 1035, 756, 667, 530, 458. MS (ESI): 282 $[M]^{+\$}$. *Anal. Calcd* (%) for $C_{14}H_{22}N_2O_2S$: C, 59.54, H, 7.85, N, 9.91, S, 11.35. Found: C, 59.71, H, 7.81, N, 9.64, S, 11.01.

4.3.7. 4-Chloro-3-(selenenylbenzyl)-N,N-diisopropylpyridine-2-carboxamide (**7a**)

Method A: Electrophile: Benzyl chloride (1.01 g, 0.92 ml, 8 mmol). Yield: 1.0 g, (59%).

Method B: To a vigorously stirred solution of **1a** (0.962 g, 4 mmol) in dry THF at −78 °C, *n*-BuLi (1.39 N in hexane, 6.0 ml, 8 mmol) was added drop-wise. The reaction mixture was stirred for 2 h at the same temperature. To the dark red solution of the carbanion, dibenzyl diselenide (2.74 g, 8 mmol) was added and the reaction mixture was slowly brought to the room temperature and worked-up as described above. Yield: 0.71 g, (41%) m.p. 104–106 °C, ^{1}H NMR: $CDCl_3$, 400 MHz δ (ppm): 8.32–8.33 (d, J = 5.2 Hz, 1H), 7.23–7.24 (d, J = 5.2 Hz, 1H), 7.17–7.22 (m, 2H), 7.09–7.16 (m, 3H), 4.19 (s, 2H), 3.45–3.52 (m, J = 6.8 Hz, 1H), 3.33–3.39 (m, J = 6.6 Hz, 1H), 1.53–1.55 (d, J = 6.9 Hz, 6H), 1.08–1.09 (d, J = 6.6 Hz, 6H). ^{13}C NMR: $CDCl_3$, 400 MHz δ (ppm): 167.2, 163.1, 151.6, 149.9, 137.5, 129.2, 128.4, 127.1, 124.0, 122.6. ^{77}Se NMR: δ (ppm): 302.38. IR (KBr, cm^{-1}): 2968, 2363, 1631, 1542, 1475, 1424, 1368, 1324, 1212, 1039, 866, 763, 724, 594. MS (ESI): 441 $[M^{+\$}, {}^{80}Se, {}^{36}Cl]$. *Anal. Calcd* (%) for

Table 5
Crystal data collection and structure refinement parameters of compound **6b** and **7a**.

Empirical formula	$C_{14}H_{22}N_2O_2S$	$C_{19}H_{23}ClN_2OSe$
Formula weight	282.40	409.80
Temperature	293(2) K	293(2) K
Wavelength	0.71069 Å	0.71073 Å
Crystal system	Orthorhombic	Tetragonal
Space group	*P*bca	*P*-42(1)c
Unit cell dimensions		
a	14.730(5) Å	21.517(2) Å
b	13.396(5) Å	21.517(2) Å
c	15.065(5) Å	8.2988(13) Å
α	90.0(5)°.	90.0°
β	90.0(5)°.	90.0°
γ	90.0(5)°.	90.0°
Volume	2972.7(18) $Å^3$	3842.0(8) $Å^3$
Z	8	8
Density (calculated)	1.262 Mg/m^3	1.417 Mg/m^3
Absorption coefficient	0.218 mm^{-1}	2.101 mm^{-1}
F(000)	1216	1680
Crystal size	24 × 18 × 16 mm^3	0.34 × 0.32 × 0.28 mm^3
Theta range for data collection	2.46–26.50°.	1.89–25.48°.
Index ranges	$18\leq h\leq 18$, $12\leq k\leq 16$, $18\leq l\leq 18$	$26\leq h\leq 25$, $22\leq k\leq 26$, $-6\leq l\leq 10$
Reflections collected	15925	20059
Independent reflections	3072 [R(int) = 0.0591]	3554 [R(int) = 0.0905]
Completeness to theta = 25.48°	theta = 26.50°99.6%	99.8%
Absorption correction	None	None
Max. and min. transmission		0.5907 and 0.5352
Refinement method	Full-matrix least-squares on F^2	Full-matrix least-squares on F^2
Data/restraints/parameters	3072/0/180	3554/0/217
Goodness-of-fit on F^2	1.109	1.044
Final R indices [$I > 2\sigma(I)$]	$R1$ = 0.0940, w$R2$ = 0.2336	$R1$ = 0.0403, w$R2$ = 0.0826
R indices (all data)	$R1$ = 0.1093, w$R2$ = 0.2445	$R1$ = 0.0543, w$R2$ = 0.0890
Absolute structure parameter		−0.018(11)
Largest diff. peak and hole	2.593 and −0.357 e $Å^{-3}$	0.514 and −0.527 e $Å^{-3}$

$C_{19}H_{23}ClN_2OSe$: C, 55.69, H, 5.65, N, 6.83. Found: C, 55.78, H, 5.79, N, 6.66.

4.3.8. 4-Chloro-(3-selenenylethylbromide)-N,N-diisopropylpyridine-2-carboxamide (**8a**)

Electrophile: 1,2-Dibromoethane (0.75 g, 0.35 ml, 4 mmol). Yield: 0.68 g, (40%) m.p.100–102 °C, ^{1}H NMR: $CDCl_3$, 400 MHz δ (ppm): 8.44–8.45 (d, J = 5.3 Hz, 1H), 7.39–7.40 (d, J = 5.2 Hz, 1H), 3.63 (s, broad peak, 2H), 3.51–3.58 (m, J = 6.6 Hz, 1H), 3.37–3.44 (m, J = 6.6 Hz, 1H), 3.40 (s, broad peak, 2H), 1.58–1.60 (d, J = 6.6 Hz, 6H), 1.16–1.18 (d, J = 6.6 Hz, 6H). IR (KBr, cm^{-1}): 2971, 1632, 1537, 1476, 1422, 1367, 1324, 1209, 1161, 1040, 827, 728, 634, 569. MS (ESI): 427 [$M^{+\$}$, ^{80}Se, ^{35}Cl]. *Anal. Calcd* (%) for $C_{19}H_{23}ClN_2OSe$: C, 39.42, H, 4.72, N, 6.57. Found: C, 39.55, H, 4.65, N, 6.70.

4.4. Reductive cleavage of Se–Se bond in **3a**

Method A: To a vigorously stirred solution of **3a** (0.25 g, 0.4 mmol) in dry THF at 0 °C, powdered $LiAlH_4$ (2.24 g, 0.88 mmol) was added in small installments. The reaction mixture was slowly brought to room temperature and stirred for 2 h. The pale yellow solution was again cooled to 0 °C and iodomethane (0.05 ml, 0.88 mmol) was added drop-wise. The resulting solution was stirred overnight and hydrolyzed with 20 ml of water the next day. The usual workup procedure afforded **5a** in 55% (0.14 g) yield.

Method B: To a vigorously stirred solution of **3a** (0.1 g, 0.16 mmol) in absolute ethanol at 0 °C, $NaBH_4$ (0.015 g, 0.39 mmol) was added in small installments. The reaction mixture was slowly brought to room temperature and stirred for 3 h at 40 °C. The pale yellow solution was again cooled to 0 °C and iodomethane (0.025 ml, 0.44 mmol) was added drop-wise. The resulting solution was stirred overnight 40 °C and hydrolyzed with 20 ml of water the next day. The usual workup procedure afforded **5a** in 80% (0.085 g) yield.

4.5. Crystal structure determination and refinement

Single-crystal X-ray data of **6b** and **7a** were collected using graphite-monochromated Mo-$K\alpha$ radiation (λ = 0.71073 Å) 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* [26]. The program SMART was used for collecting frames of data, indexing reflections, and determining lattice parameters. The data integration and reduction were processed with SAINT [27] software. An empirical absorption correction was applied to the collected reflections with SADABS [28] using XPREP [29]. All the structures were solved by the direct method using the program SHELXS-97 [30] and were refined on F^2 by the full-matrix least-squares technique using the SHELXL-97 program package. All non-hydrogen atoms were refined with anisotropic displacement parameters in all the structure. All other relevant information about the data collection and refinement are presented in Table 5.

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Appendix. Supplementary material

CCDC Nos. 791167 (**6b**); 791168 (**7a**) contains the supplementary crystallographic data for this paper. Crystallographic data for the structure analysis have been deposited with the Cambridge Crystallographic Data Center. CCDC numbers are 791167 for 4-methoxy-3-(sulfanylmethyl)-*N*,*N*-diisopropylpyridine-2-carboxamide (**6b**) and 791168 for and 4-chloro-3-(selenenylbenzyl)-*N*,*N*-diisopropylpyridine-2-carboxamide (**7a**). Copies of this information may be obtained free of charge from the Director, 12 Union Road, Cambridge CB2 1EZ, UK, fax: +44 1223 336 033; or e-mail: deposite@ccdc.cam.ac.uk or http://www.ccdc.cam.ac.uk.

Appendix. Supplementary material

Supplementary data related to this article can be found online at doi:10.1016/j.jorganchem.2011.03.009.

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