



Synthesis and characterization of pyrimidyl- and pyrazinylselenium compounds: X-ray structure of 2,5-bis(methylselenenyl)pyrazine



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ABSTRACT

A methodology for the lithiation of pyrimidine (**1a**) was developed and used for the synthesis of pyrimidylselenium compounds. The procedure involved prior complexation of **1a** with 2.2 equiv. of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ followed by a reaction with LDA or LTMP. The pyrazinylselenium derivatives were synthesized from the direct lithiation of pyrazine (**1b**) as the BF_3 -directed lithiation failed to give the desired products. All the synthesized compounds were characterized by elemental analysis, NMR (^1H and ^{13}C) and Mass spectroscopy. In addition, 2,5-bis(methylselenenyl)pyrazine (**9b**) was characterized by single crystal X-ray crystallography.

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1. Introduction

Organoseleniums with electron-deficient heterocycles have shown tremendous potential as biologically active agents [1–5], precursors to semi-conducting materials [6–8] and synthons in organic synthesis [9,10]. The chemistry of pyridylseleniums has grown substantially in the last couple of decades [11–15], and that of pyrimidylseleniums has recently shown some activity [11,16–21]. Surprisingly, there is no report on the chemistry of pyrazinylselenium compounds. We are reporting here the synthesis and characterization of pyrimidyl- and pyrazinylselenium compounds by a methodology that involves the lithiation of pyrimidine (**1a**) and pyrazine (**1b**), respectively. The direct lithiation of unsubstituted pyrimidine has always been a challenge due to the instability of the lithiated pyrimidine species [22], whereas that of **1b** has been achieved with moderate success [22,23]. Recently, the BF_3 -directed metallation of substituted pyrimidines (2,4-dimethoxy-, 2-butoxy-pyrimidine, etc.) and pyrazines (2-chloro-, 2-bromopyrazine, etc.) has been reported with highly expensive bimetallic tetramethylpiperidine (TMP) bases, $\text{TMPZnCl} \cdot \text{LiCl}$ and $(\text{TMP})_2\text{Mg} \cdot 2\text{LiCl}$ [24]. However, there is no report on the BF_3 -directed lithiation of **1a** and **1b** with lithium diisopropylamide (LDA) or lithium

tetramethylpiperdide (LTMP). The present paper provides detailed investigation on the lithiation of **1a** and **1b** in the presence and absence of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ with LDA and LTMP as the lithiating reagents, and selenium as the electrophile.

2. Experimental

2.1. General

All the reagents and solvents were purified by standard procedures, and were freshly distilled prior to use [25]. LTMP and LDA were prepared by the reaction of *n*-BuLi with 2,2,6,6-tetramethylpiperidine and diisopropylamine, respectively [26]. All the experiments were carried out in flame-dried round bottom flasks and under moisture-free nitrogen atmosphere. ^1H and ^{13}C NMR spectra were obtained on a Bruker 400 MHz spectrophotometer in CDCl_3 . ^1H NMR and ^{13}C NMR chemical shifts were cited with respect to tetramethylsilane as the internal standard. The EI mass spectra were measured using a Shimadzu GC-Mass Spectrometer equipped with an Rtx-1MS (30 m \times 0.25 mm ID \times 0.25 μm) capillary column. Elemental analysis for C, H and N was carried out on a Vario MICRO Elementar analyzer.

2.2. 2-(Methylselenenyl)pyrimidine (**4a**)

1a (0.72 g, 0.70 mL, 9.0 mmol) was treated with a solution of $\text{BF}_3 \cdot \text{Et}_2\text{O}$ in diethyl ether (2.81 g, 2.48 mL, 19.8 mmol) at 0 °C. The

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temperature of the resulting suspension was lowered to $-78\text{ }^{\circ}\text{C}$ and LDA/LTMP (18.0 mmol) was added via cannulation. The orange solution thus formed was stirred for 15 min at $-78\text{ }^{\circ}\text{C}$ and elemental selenium (1.41 g, 18.0 mmol) was added to it. The temperature of the reaction mixture was slowly raised to the room temperature and stirring was continued till most of the selenium was dissolved. The resulting solution was re-cooled to $-78\text{ }^{\circ}\text{C}$ and reacted with iodomethane (2.56 g, 1.11 mL, 18.0 mmol). The reaction mixture was slowly brought back to the room temperature and hydrolyzed with distilled water (30 mL). The organic layer was extracted with diethyl ether and dried over anhydrous sodium sulfate. The solvent was removed using a rota-evaporator and the crude product was purified with column chromatography (silica gel 60–120 mesh, hexane/EtOAc, 50:1) to give **4a** (1.09 g, 70%, LDA and 1.12 g, 71%, LTMP) as a brownish red viscous liquid. ^1H NMR: (400 MHz, CDCl_3): δ (ppm): 8.60–8.61 (d, $J = 4.8$ Hz, 2H), 7.23–7.25 (t, 1H), 2.40 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm): 169.0, 157.6, 117.7, 6.4. MS (EI, 70 eV) m/z (relative intensity): 174 (18, $[\text{M}]^+$, ^{80}Se), 94 (100), 80 (25), 67 (6), 53 (41). *Anal. Calc.* for $\text{C}_5\text{H}_6\text{N}_2\text{Se}$: C, 34.69, H, 3.49, N, 16.18. Found: C, 34.82, H, 3.39, N, 16.27%.

2.2.1. 2-(Ethylselenenyl)pyrimidine (**5a**)

1a (0.72 g, 0.70 mL, 9.0 mmol), LDA (18.0 mmol), selenium (1.41 g, 18.0 mmol) and iodoethane (2.81 g, 1.45 mL, 18.0 mmol) were used to obtain **5a** (1.08 g, 64%) as a red viscous liquid. ^1H NMR: (400 MHz, CDCl_3): δ (ppm): 8.58–8.59 (d, $J = 4.8$ Hz, 2H), 7.20–7.22 (t, 1H), 2.91–2.96 (q, 2H), 1.41–1.44 (t, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm): 168.8, 157.5, 117.4, 23.1, 15.0. MS (EI, 70 eV) m/z (relative intensity): 188 (22, $[\text{M}]^+$, ^{80}Se), 173 (4), 159 (4), 107 (100), 79 (31), 68 (4), 53 (22). *Anal. Calc.* for $\text{C}_6\text{H}_8\text{N}_2\text{Se}$: C, 38.29, H, 4.25, N, 14.89. Found: C, 38.01, H, 4.16, N, 14.96%.

2.2.2. 2,4-Bis(methylselenenyl)pyrimidine (**6a**)

1a (0.72 g, 0.70 mL, 9.0 mmol), LDA (19.8 mmol), selenium (1.56 g, 19.8 mmol) and iodomethane (2.80 g, 1.22 mL, 19.8 mmol) were used to get **6a** (0.50 g, 21%) as a red viscous liquid. ^1H NMR: (400 MHz, CDCl_3): δ (ppm): 7.94–7.96 (d, $J = 5.2$ Hz, 1H), 6.91–6.92 (d, $J = 5.4$ Hz, 1H), 2.39 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm): 168.2, 154.0, 117.8, 6.7, 5.2. MS (EI, 70 eV) m/z (relative intensity): 268 (77, $[\text{M}]^+$, ^{80}Se), 252 (2), 185 (18), 174 (29), 108 (27), 93 (100), 79 (31), 65 (2), 52 (30). *Anal. Calc.* for $\text{C}_6\text{H}_8\text{N}_2\text{Se}_2$: C, 27.08, H, 3.03, N, 10.52. Found: C, 27.19, H, 3.16, N, 10.41%.

2.2.3. 2,4,6-Tris(methylselenenyl)pyrimidine (**7a**)

1a (0.72 g, 0.70 mL, 9.0 mmol), LDA (29.7 mmol), selenium (2.34 g, 29.7 mmol) and iodomethane (4.21 g, 1.50 mL, 29.7 mmol) were used to obtain **7a** (0.16 g, 5%) as an orange viscous liquid. ^1H NMR: (400 MHz, CDCl_3): δ (ppm): 6.98 (s, 1H), 2.45 (s, 3H), 2.42 (s, 6H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm): 168.1, 154.1, 117.2, 6.7, 5.4. MS (EI, 70 eV) m/z (relative intensity): 360 (70, $[\text{M}]^+$, ^{80}Se), 343 (59), 327 (11), 281 (41), 267 (18), 251 (17), 207 (83), 193 (19), 173 (28), 147 (29), 118 (18), 95 (82), 85 (100), 73 (88), 57 (39). *Anal. Calc.* for $\text{C}_7\text{H}_{10}\text{N}_2\text{Se}_3$: C, 23.41, H, 2.80, N, 7.80. Found: C, 23.48, H, 2.89, N, 7.88%.

2.3. General method for the preparation of selenolate anion of pyrazine (**1b**)

A solution of **1b** (1 g, 12.5 mmol) in dry THF (30 mL) was cooled to $-78\text{ }^{\circ}\text{C}$ and LDA (13.75 mmol) was added slowly via cannulation. After 15 min of stirring, elemental selenium (1.08 g, 13.75 mmol) was added to it. The temperature was slowly raised till all of the selenium was dissolved. Different electrophiles (13.75 mmol) were added to the selenolate anion at $-78\text{ }^{\circ}\text{C}$ to give the desired products.

2.3.1. 2-(Methylselenenyl)pyrazine (**4b**)

Iodomethane (1.95 g, 0.85 mL, 13.75 mmol) was used as the electrophile in the above reaction to give **4b** (1.3 g, 64%) as a pale yellow liquid. ^1H NMR (400 MHz, CDCl_3): δ (ppm): 8.55–8.56 (d, $J = 1.5$ Hz, 1H), 8.38–8.40 (dd, $J = 1.7$ and 2.4 Hz, 1H), 8.22–8.23 (d, $J = 2.6$ Hz, 1H), 2.47 (s, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm): 154.1, 145.7, 144.8, 140.1, 5.3. MS (EI, 70 eV) m/z (relative intensity): 174 (25, $[\text{M}]^+$, ^{80}Se), 132 (7), 94 (100), 79 (17), 52 (49). *Anal. Calc.* for $\text{C}_5\text{H}_6\text{N}_2\text{Se}$: C, 34.69, H, 3.49, N, 16.18. Found: C, 34.77, H, 3.55, N, 16.07%.

2.3.2. 2-(Propylselenenyl)pyrazine (**5b**)

Iodopropane (2.3 g, 1.34 mL, 13.75 mmol) was used instead of iodomethane to give **5b** (1.30 g, 53%) as a pale yellow liquid. ^1H NMR: (400 MHz, CDCl_3): δ (ppm): 8.53–8.54 (d, $J = 1.5$ Hz, 1H), 8.37–8.38 (dd, $J = 1.6$ and 2.5 Hz, 1H), 8.21–8.22 (d, $J = 2.6$ Hz, 1H), 3.17–3.20 (t, 2H), 1.77–1.86 (m, 2H), 1.02–1.06 (t, 3H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm): 154.1, 146.4, 144.9, 140.2, 23.9, 23.5, 14.4. MS (EI, 70 eV) m/z (relative intensity): 204 (6, $[\text{M}]^+$, ^{80}Se), 202 (32), 160 (90), 121 (100), 107 (24), 94 (12), 79 (63), 68 (26), 52 (83). *Anal. Calc.* for $\text{C}_7\text{H}_{10}\text{N}_2\text{Se}$: C, 41.80, H, 5.01, N, 13.92. Found: C, 42.03, H, 5.18, N, 13.81%.

2.3.3. 2-(Butylselenenyl)pyrazine (**6b**)

Iodobutane (2.53 g, 1.56 mL, 13.75 mmol) was used as the electrophile to give **6b** (1.37 g, 51%) as a pale yellow liquid. ^1H NMR: (400 MHz, CDCl_3): δ (ppm): 8.53–8.54 (d, $J = 1.5$ Hz, 1H), 8.37–8.38 (dd, $J = 1.6$ and 2.5 Hz, 1H), 8.21–8.22 (d, $J = 2.6$ Hz, 1H), 3.18–3.22 (t, 2H), 1.73–1.80 (m, 2H), 1.41–1.50 (m, 2H), 0.92–0.95 (t, 3H). ^{13}C NMR (400 MHz, CDCl_3): δ (ppm): 154.2, 146.3, 144.9, 140.2, 32.1, 25.5, 23.0, 13.0. MS (EI, 70 eV) m/z (relative intensity): 218 (5, $[\text{M}]^+$, ^{80}Se), 216 (26), 187 (8), 160 (100), 135 (44), 107 (29), 94 (21), 79 (44), 52 (51). *Anal. Calc.* for $\text{C}_8\text{H}_{12}\text{N}_2\text{Se}$: C, 44.65, H, 5.62, N, 13.02. Found: C, 44.89, H, 5.79, N, 12.89%.

2.3.4. 2-(Benzylselenenyl)pyrazine (**7b**)

(Chloromethyl)benzene (1.74 g, 1.58 mL, 13.75 mmol) was used as the electrophile to obtain **7b** (1.30 g, 44%) as a dark reddish liquid. ^1H NMR: (400 MHz, CDCl_3): δ (ppm): 8.50–8.51 (d, $J = 1.6$ Hz, 1H), 8.42–8.43 (dd, $J = 1.7$ and 2.5 Hz, 1H), 8.24–8.25 (d, $J = 2.6$ Hz, 1H), 7.34–7.37 (dd, $J = 1.5$ and 5.1 Hz, 2H), 7.25–7.29 (td, $J = 1.5$ and 5.1 Hz, 1H), 7.18–7.22 (dd, $J = 1.4$ and 4.5 Hz, 2H), 4.44 (s, 2H). ^{13}C NMR (400 MHz, CDCl_3): δ (ppm): 153.9, 146.2, 144.9, 140.7, 138.3, 129.0, 128.6, 128.5, 128.4, 127.2, 29.1. MS (EI, 70 eV) m/z (relative intensity): 250 (4, $[\text{M}]^+$, ^{80}Se), 169 (35), 132 (9), 91 (100), 65 (20), 52 (9). *Anal. Calc.* for $\text{C}_{11}\text{H}_{10}\text{N}_2\text{Se}$: C, 52.80, H, 4.00, N, 11.20. Found: C, 52.92, H, 4.06, N, 11.27%.

2.3.5. Bis(2-pyrazinylselenium)methane (**8b**)

Diiodomethane (1.80 g, 0.55 mL, 6.87 mmol) was used as the electrophile to generate **8b** (1.13 g, 27%) as a light red solid. M.P. $94\text{--}97\text{ }^{\circ}\text{C}$. ^1H NMR: (400 MHz, CDCl_3): δ (ppm): 8.66–8.68 (dd, $J = 2.5$ and 3.8 Hz, 2H), 8.45–8.46 (dd, $J = 1.6$ and 4.2 Hz, 2H), 8.28–8.30 (dd, $J = 2.6$ and 5.6 Hz, 2H), 4.85 (s, 2H). ^{13}C NMR (100 MHz, CDCl_3): δ (ppm): 154.1, 146.4, 144.9, 140.2, 14.4. MS (EI, 70 eV) m/z (relative intensity): 332 (2, $[\text{M}]^+$, ^{80}Se), 253 (4), 173 (74), 161 (13), 132 (10), 119 (3), 106 (5), 93 (37), 79 (65), 66 (4), 52 (100). *Anal. Calc.* for $\text{C}_9\text{H}_8\text{N}_4\text{Se}_2$: C, 32.53, H, 2.40, N, 16.86. Found: C, 32.77, H, 2.51, N, 16.91%.

2.4. 2,5-Bis(methylselenenyl)pyrazine (**9b**)

1b (1 g, 12.5 mmol), LDA (27.5 mmol), selenium (2.18 g, 27.5 mmol) and iodomethane (3.90 g, 1.71 mL, 27.5 mmol) were used to obtain **9b** (0.38 g, 12%) as a colorless crystalline solid. M.P. $108\text{--}110\text{ }^{\circ}\text{C}$. ^1H NMR: (400 MHz, CDCl_3): δ (ppm): 8.40

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