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Synthesis of C-6 and C-3 substituted chalcogen derivatives of 2-methoxypyridine through lithiation of 2-methoxypyridine: An experimental and quantum chemical study

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ABSTRACT

A convenient methodology which can be tailored to incorporate a chalcogen atom at the C-6 or C-3 position of 2-methoxypyridine (**1**) was developed. This was achieved by the regioselective lithiation of **1** in the presence and absence of $BF_3{\cdot}Et_2O$. The reactions of the 2-methoxypyridine-BF_3 adduct with lithium diisopropylamide (LDA) and subsequent trapping with chalcogen and iodomethane furnished a C-6 substituted product. However, the use of uncomplexed **1** led to the lithiation and chalcogenation at the C-3 position. The origin of selectivity in these reactions was studied by quantum chemical analysis. It was found that the coordination between the lithium (on C-6) and the fluoride of BF_3 preponderates over the directed metalation ability of the methoxy unit in directing the lithiation process.

1. Introduction

Pyridylselenium and -tellurium compounds have shown immense potential as biological active agents [1–6], reagents for organic synthesis [7,8] and precursor to semiconducting materials [9,10]. Considerable efforts have been devoted for developing new methodologies for the synthesis of pyridylchalcogen compounds [11–13]. Methyl and halogen substituted pyridylchalcogens have been extensively studied [1,2,14–17], however to the best of our knowledge, there is no report on the synthesis of chalcogen derivatives of 2-methoxypyridine. The present study was undertaken to develop a convenient methodology which can be tailored for incorporating a chalcogen atom at the C-6 or C-3 position of 2-methoxypyridine. The lithiation route was chosen for achieving this objective. Lithiation of 2-methoxypyridine (**1**) is challenging and has been achieved with varied success [18–24]. The reaction of **1** with *n*-BuLi is limited by two competing reactions; lithiation at the C-3 position and parallel nucleophilic addition reaction at the C-6 position [19,20]. The reaction of **1** with LDA affords lithiation at the C-3 position, which is aided by the directed metalation ability of the methoxy unit. However, the utility of this methodology is restricted to a very few electrophiles as in many instances electrophiles such as iodomethane, iodine, benzaldehyde, etc., react with LDA due to a slow rate of deprotonation of **1** [20]. Complexing lithiating reagents such as *n*-BuLi-LDMAE and $TMSCH_2Li$-LDMAE affords lithiation at the C-6 position [21–25]. However, the excess amount of the base used is a limitation in this methodology as it necessitates the use of excessive amount of the electrophilic reagent, such as selenium and tellurium. This creates difficulty in the purification procedure and adds to the cost of the reaction. We have recently developed a methodology involving the BF_3 controlled selective ring lithiation of picolines, lutidines and 3-halopyridines for the synthesis of the corresponding chalcogen compounds [14,16,17]. The present study explores the utility of BF_3-aided and unaided lithiation of **1** for the incorporation of a chalcogen atom at different positions. We wanted to observe whether; (1) the complexing ability of the fluoride in BF_3 preponderates over the directed metalation ability of the methoxy unit and affords lithiation and chalcogenation at the C-6 position of 2-methoxypyridine, and (2) the slow rate of deprotonation of **1** hinders the effective insertion of the chalcogen atom into the 2-methoxypyridine scaffold. The experimental results and the origin of selectivity in these reactions were investigated with the aid of quantum chemical analysis.

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2. Experimental section

2.1. General

2-Methoxypyridine, $BF_3{\cdot}Et_2O$ and tellurium were obtained from sigma–aldrich, and *n*-BuLi was obtained from Ranbaxy, India. Selenium, diisopropylamine, THF and diethyl ether were procured from S.D. fine chemicals, India. All experiments were carried out in dry oxygen-free nitrogen atmosphere and the solvents were dried before use [26]. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrophotometer in $CDCl_3$ using tetramethylsilane (TMS) as an internal standard. EI mass spectra were taken by using a Shimadzu GC-Mass Spectrometer [GCMS QP-2010 plus] with Rtx-1MS (30 m × 0.25 mm × 0.25 μm) capillary column. The ^{77}Se and ^{125}Te NMR spectra were recorded in $CDCl_3$ using bis(methyl)diselenide and bis(methyl)ditelluride as external standards on a JNM-ECS400 spectrophotometer. The elemental analysis was carried out by using ElemantarVario MICRO analyzer.

2.2. Quantum chemical study

Quantum chemical study of **1** was carried out by Density Functional Theory (DFT) with Becke3, Lee, Yang, Parr (B3LYP) level of theory in combination with the 6-31+G(d) basis set using the GAUSSIAN 03 software package [27]. A scaling factor of 0.9806 was used for thermal corrections to Gibbs free energy. Solvent level optimization studies were performed using the IEF-PCM solvent model for Et_2O [28]. Two units of the model solvent dimethyl ether were used to study the explicit solvent effect in the reaction. The ab initio geometries were employed for calculating the solvation free energies by using the B3LYP/6-31+G(d) level. The calculation was used to obtain the pK_a values according to the equation given below [29,30]:

$$pK_a = \Delta G_R/2:303RT$$

2.3. General method for the preparation of selenolate anion at the C-6 position of 2-methoxypyridine (1)

A three-necked 100 mL RBF fitted with take-off adapter was flame dried under vacuum on a Schlenk line with four ports. The flame dried flask was slowly brought to the room temperature and the vacuum was released under nitrogen. A solution of **1** (1.03 g, 1 mL, 9.45 mmol) in dry THF (35 mL) was taken in the flask and cooled to 0 °C. The solution was purged with nitrogen gas and $BF_3{\cdot}Et_2O$ (1.47 g, 1.28 mL, 10.39 mmol) was added to it. The temperature of the resulting suspension was lowered to −78 °C and LDA (12.28 mmol) was added via cannulation. The resulting reddish solution was then stirred for 15 min at −78 °C. Elemental selenium (0.97 g, 12.28 mmol) was added to the above solution at −78 °C. The temperature was raised slowly until most of selenium was dissolved. The blackish brown solution containing the selenolate anion (**2a**) was again cooled to −78 °C and different electrophiles were added to it.

2.3.1. 2-Methoxy-6-(methylselenenyl)pyridine (3a)

Iodomethane (1.74 g, 0.76 mL, 12.28 mmol) was added to the selenolate anion (**2a**) at −78 °C. The reaction mixture was slowly brought to room temperature and hydrolyzed with distilled water (20 mL). The crude product was extracted with diethyl ether (50 mL × 3) and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed over a rota-evaporator and the crude product was purified by column chromatography (60–120 mesh silica gel, hexane–ethyl acetate, 20:1). Yield: 1.05 g (54%), yellow viscous liquid. ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.30–7.34 (t, 1H), 6.85–6.87 (dd, *J* = 2.6, 7.6 Hz, 1H), 6.43–6.45 (d, 8.1 Hz, 1H), 3. 93 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ(ppm): 163.7, 152.6, 138.4, 116.8, 106.3, 53.4, 5.3. ^{77}Se NMR (400 MHz, $CDCl_3$) δ(ppm): 373.7. MS (EI, 70 eV) *m/z* (relative intensity): 205 (6) 203 (32) 123 (100), 108 (15), 93 (30), 80 (14), 65 (13), 53 (6). *Anal.* Calc. for C_7H_9NOSe: C, 41.37, H, 4.43, N, 6.89. Found: C, 41.07, H, 4.49, N, 6.99(%).

2.3.2. Bis(2-methoxy-6-pyridyl)diselenide (4a)

The reaction mixture containing the selenolate anion, **2a**, was slowly brought to room temperature, hydrolyzed and exposed to aerial oxidation for 30 min, and then worked-up and purified. Yield: 0.68 g (38%), yellow viscous liquid. ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.38–7.42 (t, 2H), 7.32–7.34 (dd, *J* = 0.4, 7.3 Hz, 2H), 6.49–6.51 (dd, *J* = 0.5, 8.0 Hz, 2H), 3.09 (s, 6H). ^{13}C NMR (400 MHz, $CDCl_3$) δ(ppm): 163.4, 151.1, 139.3, 116.0, 107.9, 53.7. ^{77}Se NMR (400 MHz, $CDCl_3$) δ(ppm): 449.9. MS (EI, 70 eV) *m/z* (relative intensity): 380 (3), 378 (27), 376 (83), 268 (4), 188 (64), 186 (35), 108 (92), 82 (1), 80 (100), 78 (69). *Anal.* Calc. for $C_{12}H_{12}N_2O_2Se_2$: C, 38.29, H, 3.19, N, 7.44. Found: C, 38.21, H, 3.07, N, 7.58(%).

2.3.3. 6-(Benzylselenenyl)-2-methoxypyridine (5a)

(Chloromethyl)benzene (1.41 g, 1.28 mL, 12.28 mmol) was added to a solution containing **2a** at −78 °C. The reaction mixture was slowly brought to room temperature, hydrolyzed and purified. Yield: 1.05 g (40%), yellow liquid. ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.29–7.32 (t, *J* = 6.1 Hz, 1H), 6.88–6.90 (d, *J* = 7.2 Hz, 1H), 6.45–6.49 (d, *J* = 8.4 Hz, 1H), 7.16–7.38 (m, 6H), 3.97 (s, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ(ppm): 163.8, 151.4, 139.8, 139.3, 138.4, 128.9, 128.5, 128.3, 128.8, 115.9, 107.5, 53.7, 34.0. MS (EI, 70 eV) *m/z* (relative intensity): 281 (2), 279 (9), 277 (4), 188 (1), 108 (2), 91 (100). *Anal.* Calc. for $C_{13}H_{11}NOSe$: C, 55.91, H, 3.94, N, 5.01. Found: C, 55.61, H, 3.84, N, 5.11(%).

2.4. General method for the preparation of selenolate/tellurolate anion at the C-3 position of 2-methoxypyridine (1)

A solution of **1** (1.03 g, 1 mL, 9.45 mmol) in dry THF (30 mL) was cooled to 0 °C in a three-necked 100 mL RBF. A solution of LDA (12.28 mmol) in dry THF was added to it in a drop-wise manner via cannulation. The resulting red solution was stirred for 1 h at 0 °C. The temperature of the solution, containing the carbanion **1-L**, was lowered to −78 °C. Selenium (0.97 g, 12.28 mmol) or tellurium powder (1.56 g, 12.28 mmol) was added to this solution. The temperature of the reaction mixture was raised slowly till most of selenium/tellurium was dissolved. The blackish brown solution, containing the selenolate/tellurolate anion (**2b-Se/Te**), was again cooled to −78 °C and different electrophiles were added to it to give the desired product.

2.4.1. 2-Methoxy-3-(methylselenenyl)pyridine (3b)

Iodomethane (1.74 g, 0.76 mL, 12.28 mmol) was added to **2b-Se** at −78 °C. The reaction mixture was slowly brought to room temperature, hydrolyzed and purified as described for **3a**. Yield: 1.50 g (81%), yellow liquid. ^1H NMR (400 MHz, $CDCl_3$) δ(ppm): 7.96–7.98 (dd, *J* = 1.6, 4.9 Hz, 1H), 7.45–7.47 (dd, *J* = 1.6, 7.4 Hz, 1H), 6.82–6.85 (dd, *J* = 4.9, 7.4 Hz, 1H), 4.00 (s, 3H), 2.26 (s, 3H). ^{13}C NMR (400 MHz, $CDCl_3$) δ(ppm): 160.9, 143.4, 136.4, 117.6, 116.4, 53.9, 4.7. ^{77}Se NMR (400 MHz, $CDCl_3$) δ(ppm): 254.2. MS (EI, 70 eV) *m/z* (relative intensity): 205 (18), 203 (100), 188 (85), 172 (3), 158 (30), 108 (99). *Anal.* Calc. for C_7H_9NOSe: C, 41.37, H, 4.43, N, 6.89. Found: C, 41.57, H, 4.41, N, 6.79(%).