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Regioselective Synthesis of 4-Bromo-3-formyl-*N*-phenyl-5-propylthiophene-2-carboxamide

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Abstract: We synthesized 4-bromo-3-formyl-*N*-phenyl-5-propylthiophene-2-carboxamide by using three successive direct lithiations and a bromination reaction starting from thiophene. All these lithiation reactions were carried out at −78 °C to RT over a period of 1 to 24 h based on the reactivity of electrophile. This is a four-step protocol starting from thiophene with an overall yield of 47%.

Keywords: thiophene; regioselective; *n*-BuLi; lithiation

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1. Introduction

Functionalized derivatives of thiophene have massively contributed to the growth of chemistry materials which have shown promising developments towards new technologies in electronics [1–5]. At the same time, thiophene-derived small organic molecules have shown a wide variety of applications including agrochemical [6,7] and pharmaceutical [8–10] fields. The model organic compound 4-bromo-3-formyl-*N*-phenyl-5-propylthiophene-2-carboxamide (Figure 1) is very useful, with functionalization that allows facile downhill derivation, as well as handles that themselves can be derivatized to the target material. This system benefits from new directed derivations that have not previously been reported, leading to three new characterized derivatives. The aldehyde group in position 3 gives bench-stable derivatives that are accessible for enhanced synthetic modification. The amide group at position 2 contributes to the ease of functionalization for product 4 (Scheme 1) and can be deprotected for further functionalization. The novelty of this model system is the presence of a bromo functionality at position 4, which is a useful handle for halogen exchange or coupling chemistry. Thiophene derivatives are traditionally synthesized by aromatic electrophilic substitution [11], by heterocyclization methods [12], metal halogen exchange [13–16] or palladium chemistry [17–20], but these approaches require additional transformations, which results in increased number of steps and overall lower yield in total synthesis. Therefore, we have established a new synthetic protocol for a synthesis of tetra-substituted thiophene derivative, which promotes a series of functionalizations that would streamline synthesis of complex tetra-substituted thiophenes. In this study we report a chemo and regioselective synthesis of tetra substitute thiophene derivative by using three successive direct lithiations and a bromination on thiophene ring.

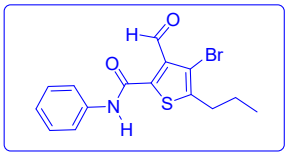
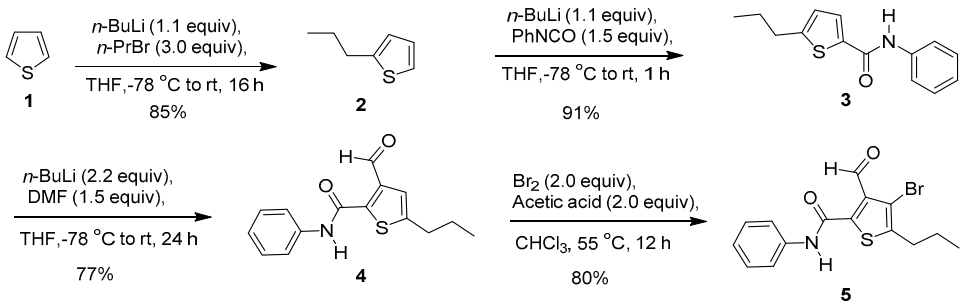


Figure 1. 4-Bromo-3-formyl-*N*-phenyl-5-propylthiophene-2-carboxamide.



Scheme 1. Synthesis of 4-bromo-3-formyl-*N*-phenyl-5-propylthiophene-2-carboxamide.

2. Results and Discussion

First, 4-bromo-3-formyl-*N*-phenyl-5-propylthiophene-2-carboxamide **5** was prepared from thiophene by three consecutive chemo and regioselective direct lithiation reactions and a bromination reaction as shown in Scheme 1. Then, 2-Propylthiophene **2** was prepared by lithiation of thiophene **1** by using *n*-BuLi (1.1 equiv.) and *n*-propyl bromide in THF following the literature procedure [21] to give 85%. This reaction required lithiation of thiophene at −78 °C utilizing *n*-BuLi over a period of 1 h and was followed by reaction with *n*-PrBr to furnish 2-propylthiophene **2**. Next, 2-propylthiophene **2** was treated with *n*-BuLi for lithiation at −78 °C followed by reaction with phenylisocyanate to get *N*-phenyl-5-propylthiophene-2-carboxamide **3** in 91%. This regioselectivity is consistent with the literature report [22] where a similar reaction was carried out with 2-hexylthiophene in presence of *n*-BuLi and CO_2 to get 5-hexylthiophene-2-carboxylic acid. We observed that one thiophene *C-H* proton of compound **3** appeared as a doublet at 7.50 ppm with a coupling constant of 3.2 Hz, whereas another *C-H* proton appeared as a multiplet at 6.80–6.79 ppm.

Amide directed lithiation by using *n*-BuLi of *N*-phenyl-5-propylthiophene-2-carboxamide **3** and subsequent quenching with DMF gave the desired 3-formyl-*N*-phenyl-5-propylthiophene-2-carboxamide **4** in 77%. The thiophene *C-H* proton of compound **4** appeared as a singlet at 7.29 ppm, characteristic of a tri-substituted thiophene [13]. Finally, the bromination reaction on **4**, carried out using two equiv. of Br_2 and acetic acid in $CHCl_3$, provided 4-bromo-3-formyl-*N*-phenyl-5-propylthiophene-2-carboxamide **5** with 80%.

3. Materials and Methods

All reactions were conducted using oven-dried glassware under an atmosphere of Argon (Ar). Commercial grade reagents were used without further purification. Commercially available anhydrous solvents were used. Flash chromatography was carried out using silica gel (230–400 mesh). TLC was performed on aluminum-backed plates coated with Silica gel 60 with F254 indicator. NMR spectra were recorded on Brucker 200 MHz and Brucker 400 MHz spectrometers at department of chemistry, Indian Institute of Technology Kharagpur, India; ^{1}H NMR chemical shifts are expressed in parts per million (δ) relative to $CDCl_3$ (δ = 7.26) and ^{13}C NMR chemical shifts are expressed in parts per million (δ) relative to the $CDCl_3$ resonance (δ = 77.0). Melting points (m.p.) of solid compounds were reported without correction. Elemental analyses were carried out on a Perkin-Elmer 2400-II (Indian Institute of Technology Kharagpur). LCMS were recorded on Waters ACQUITY UPLC with PDA (200–500 nm) and ELSD detectors at department of chemistry, Indian Institute of Technology, Kharagpur, India.

3.1. Synthesis of 2-Propylthiophene **2**

Thiophene (119 mmol, 10.0 g) and 120 mL THF were taken in 250 mL of a round-bottom flask and cooled to −78 °C. A total of 52.3 mL of *n*-BuLi (131 mmol, 1.1 equiv., 2.5 M in hexane) was added dropwise at same temperature and stirred for 45 min. Then, 43.2 g propyl bromide (360 mmol, 3 equiv.) was added slowly. It was warmed to rt and stirred for 16 h. Upon completion of the reaction, it was quenched with saturated ammonium

chloride and extracted with ethyl acetate (250 mL). The organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (hexane) gave the titled compound color less liquid (12.5 g, 85% yield). Observed NMR data are in good agreement with the literature [21]; ^{1}H-NMR ($CDCl_3$, 200 MHz): 7.11 (d, *J* = 3.8 Hz, 1H), 6.93 (dd, *J* = 3.4, 5.0 Hz, 1H), 6.80 (m, 1H), 2.82 (t, *J* = 7.4 Hz, 2H), 1.74 (dd, *J* = 7.4, 14.8 Hz, 2H), 0.99 (t, *J* = 7.4 Hz, 3H).

3.2. Synthesis of N-Phenyl-5-propylthiophene-2-carboxamide **3**

Next, 2-Propylthiophene **2** (79.3 mmol, 10.0 g) and 80 mL THF were taken in 250 mL round-bottom flask and cooled to −78 °C. A total of 34.9 mL *n*-BuLi (87.2 mmol, 1.1 equiv., 2.5 M in hexane) was added slowly at −78 °C and stirred for 45 min. Then, 14.1 g phenyl isocyanate (119 mmol, 1.5 equiv.) taken in 25 mL THF was added slowly. It was warmed to rt and stirred for 1 h. Upon completion of the reaction, it was quenched with ammonium chloride and extracted with ethyl acetate (100 mL). The organic layer was washed with brine and dried over Na_2SO_4. Concentration and flash column chromatography (10% ethyl acetate in hexane) gave the titled compound as white solid (16.7 g, 91% yield). m.p. 124 °C–126 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz): 7.76 (s, 1H), 7.63–7.61 (m, 2H), 7.50 (d, 3.7 Hz, 1H), 7.37–7.33 (m, 2H), 7.16–7.12 (m, 1H), 6.80–6.79 (m, 1H), 2.85–2.81 (m, 2H), 1.79–1.70 (sextet, *J* = 7.4 Hz, 2H), 1.01 (t, *J* = 7.3 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 160.1, 152.1, 137.8, 136.1, 129.0, 128.7, 125.1, 124.3, 120.1, 32.4, 24.7, 13.5. ESI-MS (positive mode, m/z: 264 (M+ H)$^+$, 100%), 491 (2M+ H)$^+$, 20%). Anal. (CHN %) Calcd for $C_{14}H_{15}NOS$: C, 68.54; H, 6.16; N, 5.71. Found: C, 68.61; H, 6.19; N, 5.66.

3.3. Synthesis of 3-Formyl-N-phenyl-5-propylthiophene-2-carboxamide **4**

N-phenyl-5-propylthiophene-2-carboxamide **3** (40.8 mmol, 10.0 g) and 80 mL of THF were taken in 100 mL round-bottom flask and placed at −78 °C. A total of 36.0 mL of *n*-BuLi (89.7 mmol, 2.2 equiv., 2.5 M in hexane) added dropwise over 10 min and stirred for 20 min. Neat DMF (4.6 g, 61.2 mmol) was added slowly over 5 min and the reaction stirred at rt for 18 h. On completion, it was quenched with NH_4Cl and extracted with ethyl acetate (100 mL). Concentration and flash column purification (10% ethyl acetate in hexane) gave the titled compound as a yellow solid (9.1 g, 77% yield). m.p. 163 °C–166 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz): 11.89 (s, 1H), 9.88 (s, 1H), 7.82–7.80 (m, 2H), 7.4–7.36 (m, 2H), 7.29 (s, 1H), 7.16 (t, *J* = 7.4 Hz, 1H), 2.87–2.82 (m, 2H), 1.74 (dd, *J* = 7.4 Hz, 2H), 1.03 (t, *J* = 7.3 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 187.6, 158.0, 150.8, 146.4, 138.1, 135.2, 131.3, 129.0, 124.5, 120.3, 31.9, 24.4, 13.5. ESI-MS (positive mode, m/z: 274 (M+ H)$^+$, 100%), 181 (10%). Anal. (CHN %) Calcd for $C_{15}H_{15}NO_2S$: C, 65.91; H, 5.53; N, 5.12. Found: C, 65.97; H, 5.49; N, 5.17.

3.4. Synthesis of 4-Bromo-3-formyl-N-phenyl-5-propylthiophene-2-carboxamide **5**

Next, 3-Formyl-*N*-phenyl-5-propylthiophene-2-carboxamide **4** (3.6 mmol, 1.0 g), acetic acid (1 mL) and 20 mL of chloroform were charged into a 50 mL, three-necked flask equipped with a stirrer, a dropping funnel and an outlet for the hydrogen bromide evolution. Bromine (7.3 mmol, 1.1 g) was added dropwise to the stirred mixture over a period of 10 min in ice cold conditions. Then, the reaction mixture was warmed to room temperature. It was heated at 50 °C for 24 h. The reaction mixture was quenched with $NaHCO_3$ and extracted with EtOAc. The organic layer was separated, washed with water, dried over Na_2SO_4. Concentration and flash column chromatography (20% ethyl acetate in hexane) gave the titled compound as a light-yellow solid (1.0 g, 80% yield). m.p. 146 °C. ^{1}H-NMR ($CDCl_3$, 400 MHz): 12.01 (s, 1H), 9.86 (s, 1H), 7.71 (dd, *J* = 8.8 Hz, 2.04 Hz, 2H), 7.4–7.29 (dd, 8.8 Hz, 2.0 Hz, 2H), 7.30 (s, 1H), 2.87–2.83 (m, 2H), 1.74 (sextet, *J* = 7.4 Hz, 2H), 1.03 (t, *J* = 7.3 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 100 MHz): 187.6, 158.0, 151.2, 146.0, 137.2, 135.1, 132.0, 131.5, 121.8, 117.1, 31.9, 24.4, 13.5. ESI-MS (negative mode, m/z: 350 (M-H)$^-$, 100%), 312 (15%), 145 (15%). Anal. (CHN %) Calcd for $C_{15}H_{14}BrNO_2S$: C, 51.15; H, 4.01; N, 3.98. Found: C, 51.18; H, 4.02; N, 3.91.

4. Conclusions

This protocol utilizes the three successive chemo and regioselective lithiation reactions and one bromination reaction to generate tetra-substituted thiophene, which can then be utilized for further derivation for numerous applications. We synthesized 4-bromo-3-formyl-*N*-phenyl-5-propylthiophene-2-carboxamide from thiophene in only four steps with an overall yield of 47%.

Supplementary Materials: The following are available online, Figure S1: ^{1}H-NMR spectrum of compound **2**; Figure S2: ^{1}H-NMR spectrum of compound **3**; Figure S3: ^{1}H-NMR spectrum of compound **3**; Figure S4: ^{1}H-NMR spectrum of compound **4**; Figure S5: ^{13}C-NMR spectrum of compound **4**; Figure S6: DEPT-135 spectrum of compound **4**; Figure S7: LCMS analysis (chromatogram and ionization) compound **4**; Figure S8: LCMS analysis (mass, positive mode) compound **4**; Figure S9: ^{1}H-NMR spectrum of compound **5**; Figure S10: ^{13}C-NMR spectrum of compound **5**; Figure S11: DEPT-135 spectrum of compound **5**; Figure S12: LCMS analysis (chromatogram and ionization) compound **5**; Figure S13: LCMS analysis (mass, negative mode) compound **5**; Figure S14: LCMS analysis (chromatogram and ionization) compound **3**; Figure S15: LCMS analysis (mass, negative mode) compound **3**.

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Conflicts of Interest: The authors declare no conflict of interest.

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