



A selective and direct synthesis of 2-bromo-4-alkylthiophenes: Convenient and straightforward approaches for the synthesis of head-to-tail (HT) and tail-to-tail (TT) dihexyl-2,2'-bithiophenes

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ABSTRACT

A straightforward method for the synthesis of 2-bromo-4-alkylthiophenes was developed, and the desired products were obtained in the highest chemical yields (>90%) reported to date. 2-Bromo-4-alkylthiophenes were synthesized by regioselective lithiating of 3-alkylthiophenes with *n*-BuLi and quenching with bromine at -78 °C. Moreover, a simple and efficient protocol for the synthesis of dihexyl-2,2'-bithiophenes was developed by employing 2-bromo-4-hexylthiophene instead of the commonly used monomer, 2-bromo-3-hexylthiophene. Kumada and Suzuki cross-coupling reactions were conducted to synthesize the desired products as head-to-tail (HT) and tail-to-tail (TT) regioisomers in high yields and excellent selectivity.

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Oligo- and polythiophenes have received substantial attention as potential materials in photovoltaic and electroluminescence devices.¹ Poly(3-alkylthiophenes) (P3ATs) are one of the most extensively studied conductive polymers of the past decade due to their high solubility and interesting electrochemical and physical properties.² Recently, oligo- and poly-3ATs with dramatically improved properties have been produced by a regioregular synthesis.^{3,4} The substrates used in the preparation of oligo- and poly-3ATs are neither centrosymmetric nor do they possess a symmetry axis; thus, three possible isomeric diads can be formed from the coupling of 3-alkylthiophenes. As a result, four types of spectroscopically distinct nonequivalent triads are detected in the NMR spectra.^{4–7} However, head-to-head couplings are unfavorable due to steric repulsion between the alkyl chains and the lone pairs of electrons on the adjacent sulfur atoms.^{4,6,7} Thus, an efficient synthesis of alkylthiophenes would provide access to oligo- and polythiophenes, which may lead to the development of new devices and applications of polymer-based materials.

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Kumada^{4,6,8,9} and Suzuki¹⁰ cross-coupling methods have been used extensively for the synthesis of head-to-tail and tail-to-tail oligo- and poly-ATs. Alternatively, cryogenic lithiation of 2-halo-3-alkylthiophenes and the subsequent treatment with organotin or organoboron electrophiles is an efficient method for generating monomers for the regiospecific synthesis of oligo- and poly-ATs.^{4,11,12} Thus, halothiophenes are one of the most important structures for the homocoupling of thiophenes. Upon treatment with a stoichiometric amount of *N*-bromosuccinimide, 3-alkylthiophenes quantitatively transformed into 2-bromo-3-alkylthiophenes.^{13,14} The reaction is complete within a few minutes at ambient or slightly elevated temperatures, and overbromination typically leads to the corresponding 2,5-dibromo-3-alkylthiophenes.¹⁴ Although brominating the α -position of 3-alkylthiophenes has been investigated extensively, few methods allow for the selective bromination of the 5th position of 3-alkylthiophenes.^{6,15}

Reinecke et al. have investigated the bromination of 3-methylthiophene by reacting the substrate with *n*-BuLi and quenching with bromine.^{15b} An inseparable mixture of products was obtained, and the desired product (2-bromo-4-methylthiophene) was difficult to isolate in reasonable yield and purity.^{15b} Interestingly, de Meijere et al. have also recently reported on the synthesis of 2-bromo-4-methylthiophene in 55% yield by lithiating 3-methylthiophene with

n-BuLi followed by treating the resulting 2-lithio-4-methyl derivative with *N,N,N',N'*-tetramethyl-1,2-ethylenediamine (TMEDA) and quenching with CBr₄.^{15d}

As shown in Scheme 1, McCullough and co-workers synthesized 2-bromo-4-butylthiophene (**5a**) in four distinct steps starting from 3-butylthiophene (**1a**).⁶ To generate 2-bromo-4-butylthiophene, the TMS-blocking group was removed from 2-trimethylsilyl-3-butyl-5-bromothiophene (**4**) and the desired product **5a** was obtained in 73% yield. Moreover, the synthesis of 2-bromo-4-dodecylthiophene has been achieved by lithiating 3-dodecylthiophene and reacting the lithiated intermediate with carbon tetrabromide (CBr₄).⁶ The crude product mixture consisted of 3-dodecylthiophene and both isomers of the desired product in a 9:1 ratio. However, due to side reactions and poor recovery, the overall yield of 2-bromo-4-dodecylthiophene was very low (23%).

Recently, Luscombe et al. synthesized 2-bromo-4-hexylthiophene (**5b**) by lithiating 3-hexylthiophene (**1b**) with *n*-BuLi followed by treating the lithiated intermediate with TMEDA and CBr₄ (Scheme 2).^{15e} However, after fractional distillation, the desired product was obtained in only ~11% yield.

Due to the limitations in the aforementioned synthesis, we developed an efficient and straightforward method for the synthesis of 2-bromo-4-alkylthiophenes, and obtained the highest chemical yields reported to date. Moreover, Kumada and Suzuki cross-coupling of 2-bromo-4-hexylthiophene was conducted to synthesize dihexyl-2,2'-bithiophenes in high chemical yields and excellent selectivity.

Lithiation of 3-alkylthiophenes occurs predominantly at the carbon- γ to the alkyl chain, however, sterically hindered alkyl substituents increase the selectivity of lithiation.^{6,11,12,15e} Thus, 3-alkylthiophenes (**1a–c**) were lithiated with *n*-BuLi at -78°C and subsequently quenched with bromine at the same temperature. 2-Bromo-4-alkylthiophenes (**5a–c**) were produced, along with trace amounts of 2,5-dibromo-3-alkylthiophenes (**6a–c**) (Scheme 3). After the addition of bromine, the color of the reaction mixture changed within only few minutes, indicating the reaction was completed. A slight excess of bromine ensured complete conversion to the desired product.

When bromine was added to the reaction mixture in one portion at -78°C or at elevated temperatures, the desired products **5a–c** were formed in low to moderate yields (43–67%) due to scrambling at the α -carbon adjacent to the alkyl groups of **1a–c** by hydrogen–bromide exchange.^{12–14} Significant amounts of the starting material **1**, as well as 2-bromo- and 2,5-dibromo-3-alkylthiophenes (**2** and **6**, respectively), were detected and fully characterized. Very slow addition of Br₂ (as a solution in THF) was necessary to achieve satisfactory results. Moreover, after the complete addition of bromine, when water and/or aqueous NaOH was added to the reaction mixture, at ambient or even lower temperature, the desired products **5a–c** were obtained in low yields as a mixture of isomeric products. To achieve selective formation of the desired products, the reaction must be ended at -78°C . It was realized that adding a few drops of an aqueous methanolic solution of sodium thiosulfate at -78°C was found to be a suitable method for ending the reaction. These modifications provided 2-bromo-4-alkylthiophenes (**5a–c**) in high yields (>90%). Several attempts to isolate the desired products **5a–c** by fractional

distillation failed to afford good yields; however, the desired products could be obtained in excellent purity with high yields by careful silica gel flash chromatography.

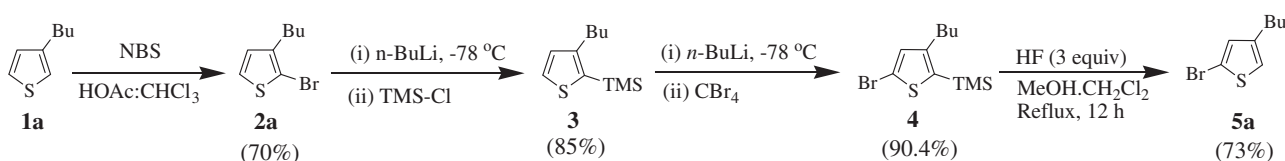
The structure of 2-bromo-4-alkylthiophenes (**5a–c**) was characterized and confirmed by each of ¹H and ¹³C NMR spectroscopy (see Supplementary data). The ¹H and ¹³C NMR spectra of the resulting 2-bromo-4-alkylthiophenes were fully consistent with the expected structures.

Kumada cross-coupling of thienylmagnesium bromides and bromothiophenes is a useful method for the homologation of thiophenes and the synthesis of oligo- and polythiophenes.^{4,6,8,9} Thus, we attempted the biaryl coupling of 3-hexylthiophene according to the Kumada cross-coupling procedure. 2-Bromo-4-hexylthiophene (**5b**) reacted readily with magnesium, resulting in the exclusive formation of 4-hexyl-2-thienylmagnesium bromide (**7**) (Scheme 4). To verify the formation of the Grignard reagent **7** in a good yield, **5b** was reacted with magnesium and quenched with 2 M HCl. Nearly quantitative conversion to 3-hexylthiophene (**1b**) was observed, along with a negligible amount of 2-bromo-4-hexylthiophene (**5b**), as shown by GC–MS, ¹H, and ¹³C NMR analyses.

Kumada cross-coupling of the intermediate **7** with **2b** and/or **5b** in the presence of catalytic amounts of Ni(dppp)Cl₂ yielded exclusively the corresponding coupled products 3,4'-dihexyl-2,2'-bithiophene (**8**) and 4,4'-dihexyl-2,2'-bithiophene (**9**), in high yields (Scheme 4). The coupled product **8** was also readily prepared in high yield (92%) via Kumada cross-coupling of 3-hexyl-2-thienylmagnesium bromide (**10**)^{5h,13,15} and **5b** in the presence of catalytic amounts of Ni(dppp)Cl₂ (Scheme 4). It is worth to mention that bithiophenes **8** and **9** have not been synthesized by this synthetic pathway; however, 3,4'-dihexyl-2,2'-bithiophene (**8**) was previously prepared in 75% yield by a metal-free oxidative biaryl-coupling reaction of 3-hexylthiophene (**1b**) and a recyclable hypervalent iodine (III) reagent in the presence of TMSBr.¹⁶ Moreover, 4,4'-dihexyl-2,2'-bithiophene (**9**) was previously prepared in 52% yield by reacting 3-hexylthiophene with *n*-BuLi at -78°C and treating the lithiated intermediate with CuCl₂.^{11a}

The reactivity of 2-bromo-4-hexylthiophene (**5b**) in the Kumada cross-coupling reaction was satisfactory. Compared to 2-bromo-3-hexylthiophene (**2b**), the bromine in 2-bromo-4-hexylthiophene (**5b**) was more reactive and the corresponding Grignard reagent was formed rapidly. However, the oxidative addition of Ni(cod)₂ (cod = 1,5-cyclooctadiene) to 2,5-dibromo-3-alkylthiophenes occurs preferentially at the fifth position of the thiophene ring due to the less amount of steric hindrance relative to the second position.^{2f,4,17} Similar to the results obtained by Grignard Metathesis Method (GRIM) for the synthesis of HH and TT-poly-ATs, the lack of steric congestion facilitates the formation of an intermediate between the bromine atom in 2-bromo-4-hexylthiophene (**5b**) and Ni(dppp)Cl₂, which leads to TT and HT couplings.^{4,6,7}

The lithiation of 2-bromo-4-hexylthiophene (**5b**) with *n*-BuLi at -78°C and the subsequent reaction with triisopropylborate and pinacol afforded 2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)-4-hexylthiophene (**11**) in excellent yield (95%, Scheme 5). However, boronic ester **11** has been previously synthesized in 89% yield by reacting 3-hexylthiophene (**1b**) with *n*-BuLi at -78°C and subsequently treating the lithiated intermediate with 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.¹¹



Scheme 1. Synthesis of 2-bromo-4-butylthiophene in four distinct steps, starting from 3-butylthiophene, with an overall yield of 73%.⁶

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