

Synthesis of Well-Defined Head-to-Tail-Type Oligothiophenes by Regioselective Deprotonation of 3-Substituted Thiophenes and Nickel-Catalyzed Cross-Coupling Reaction

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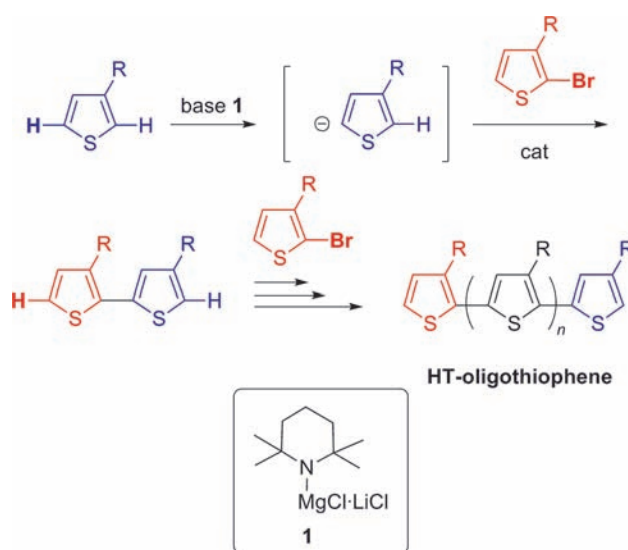
S Supporting Information

ABSTRACT: Iterative growth of thiophene oligomers by single-step extensions has been realized by regioselective metalation of 3-substituted thiophenes with the Knochel–Hauser base (TMPMgCl·LiCl) and coupling with bromothiophene using a nickel catalyst. Treatment of 3-hexylthiophene with TMPMgCl·LiCl induces metalation at the 5-position selectively. Subsequent addition of 2-bromo-3-hexylthiophene and a nickel catalyst leads to the corresponding bithiophene. The obtained bithiophene is converted to the terthiophene and then to the quaterthiophene by repeating the similar protocol. A concise synthesis of MK-1 and MK-2, which are organic dye molecules bearing an oligothiophene moiety that are used in photovoltaic cells, has been achieved.

Oligothiophenes and polythiophenes have recently attracted considerable attention in materials science as advanced organic molecules with electronic and optoelectronic characteristics. These are employed as various materials such as thin-film organic transistors,¹ liquid-crystalline compounds,² and dye-sensitized organic photovoltaic cells.³ Accordingly, the development of a concise preparative method for well-defined thiophenes is major concern in organic synthesis as well as materials science.⁴ The use of transition-metal-catalyzed cross-coupling is a highly effective strategy for the synthesis of thiophene derivatives as materials, and a variety of coupling protocols have been employed to date.⁵ Our recent interest in the functionalization of C–H bonds of heteroaromatic compounds with a transition-metal catalyst to form C–C bonds⁶ or C–heteroatom bonds⁷ is also a possible candidate for an effective synthetic pathway to such thiophenes. Indeed, we have shown synthetic methods for several oligothiophenes with C–H bond functionalization.⁸

In the context of the characteristics of thiophenes as advanced materials, it has been important to form head-to-tail (HT)-type connections between thiophene units since a variety of oligothiophene derivatives of superior performance are frequently found in the chemical structure bearing HT thiophene linkages. Much effort has been paid to the development of synthetic methodologies for HT-type oligothiophenes, which are based on stepwise cross-coupling and additional transformation sequences.⁹ Our recent approach⁸ was also based on a multistep sequence involving transition-metal-catalyzed C–H coupling to form the

Scheme 1



thiophene–thiophene linkage and subsequent halogen exchange leading toward the thiophene-extended substrate.

It is therefore intriguing to develop a simpler and more straightforward synthesis of HT oligothiophenes, which would bring about remarkably practical methodology. We thus envisaged developing a regioselective metalation of 3-substituted thiophenes by hydrogen abstraction to generate a coupling precursor for the reaction with 2-halo-3-substituted thiophenes, leading to the corresponding HT-connected bithiophene. Since we have recently shown C–H coupling polymerization of 2-halo-3-substituted thiophene using the Knochel–Hauser base TMPMgCl·LiCl (**1**; TMPH = 2,2,6,6-tetramethylpiperidine)¹⁰ or a combination of a Grignard reagent with a catalytic amount of secondary amine in the presence of a nickel catalyst,¹¹ such a reaction system would also be a potential candidate for the metalation of 3-substituted thiophenes *if it occurs in a regioselective manner at the 5-position*. In addition, the bithiophene formed would be employed directly as a substrate for further extension leading to terthiophene, and repetition of the iterative metalation/coupling sequence would serve as a highly practical synthetic pathway to well-defined HT oligothiophenes, as shown in Scheme 1. Herein we describe how the use of **1** and subsequent nickel-catalyzed

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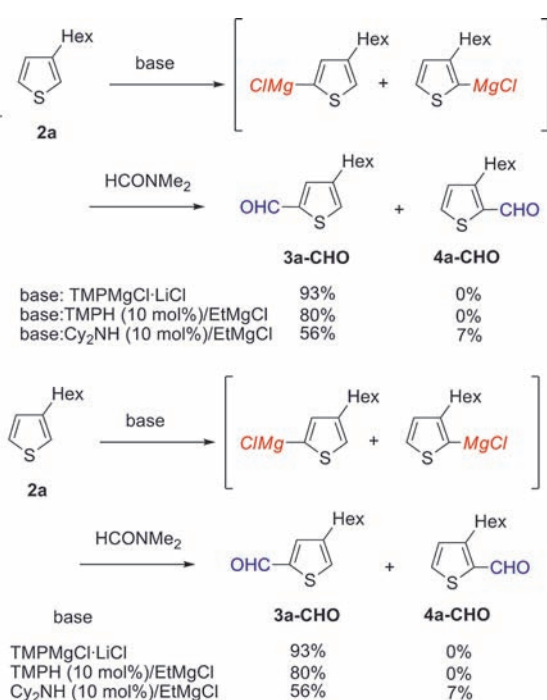
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cross-coupling effectively accomplish the extension of a thiophene unit, leading to HT oligothiophenes with high efficiency.

We first carried out the reaction of 3-hexylthiophene (**2a**) with **1** to examine the position of proton abstraction. The regioselectivity was confirmed by quenching with *N,N*-dimethylformamide (DMF) to afford 5-formyl-3-hexylthiophene (**3a-CHO**) or 2-formyl-3-hexylthiophene (**4a-CHO**). It was found that deprotonation at the 5-position took place after stirring at room temperature for 3 h, forming **3a-CHO** in 93% yield, whereas the regioisomer **4a-CHO** was not detected at all. The reaction with the combination of 10 mol % TMPH and EtMgCl also afforded **3a-CHO** predominantly, whereas the use of dicyclohexylamine (Cy_2NH), which showed excellent performance in the polymerization of chlorothiophenes,^{11b} resulted in slightly inferior regioselectivity (Scheme 2).

With regioselective metalation at the 5-position of thiophene in hand, our interest was then focused on its application to the

Scheme 2



formation of HT-type thiophene–thiophene bonds. The reaction of **2a** with 2-bromo-3-hexylthiophene (**5a**) to give bithiophene **6a** was examined using several transition-metal catalysts. As shown in Table 1, the reaction using palladium catalysts with highly electron-donating ligands proceeded in moderate yields. The reaction with 2.0 mol % $NiCl_2(dppp)$ at 60 °C for 27 h afforded **6a** in 52% yield, whereas the reaction with $NiCl_2(PPh_3)_2$ hardly proceeded. Higher catalytic activity was achieved with 2.0 mol % loadings of nickel catalysts bearing the N-heterocyclic carbene (NHC) ligands 1,3-bis(2,6-diisopropylphenyl)imidazolidin-2-ylidene (SIPr) and 1,3-bis(2,6-diisopropylphenyl)imidazole-2-ylidene (IPr),¹² which afforded **6a** in excellent yields at 60 °C, whereas the reaction with $Ni(cod)_2$ in the absence of an NHC ligand hardly proceeded. It is also remarkable that the reaction using the Ni–SIPr complex as a catalyst proceeded at room temperature in a reasonable yield. The cross-coupling of thiophenes was also found to proceed efficiently with a metalated thiophene by the reaction of a Grignard reagent and catalytic TMPH in comparable yields. Despite the use of metalation with a less selective system ($EtMgCl/Cy_2NH$), formation of bithiophene selectively took place in an HT manner accompanied by only a trace amount of head-to-head bithiophene.

The obtained HT bithiophene **6a** was subjected to further reaction with **5a** using 10 mol % TMPH and 1.5 equiv of $EtMgCl$ in a similar manner, furnishing terthiophene **7a** in 90% yield. Treatment of **7a** with **1** (1.8 equiv) followed by reaction with bromothiophene **5a** gave quaterthiophene **8a** in 65% yield. It was also found that the reaction of **6a** with monobrominated bithiophene afforded **8a** in 66% yield. In addition, terthiophene **7a** reacted with brominated terthiophene to give the corresponding sexithiophene. The results are presented in Scheme 3.

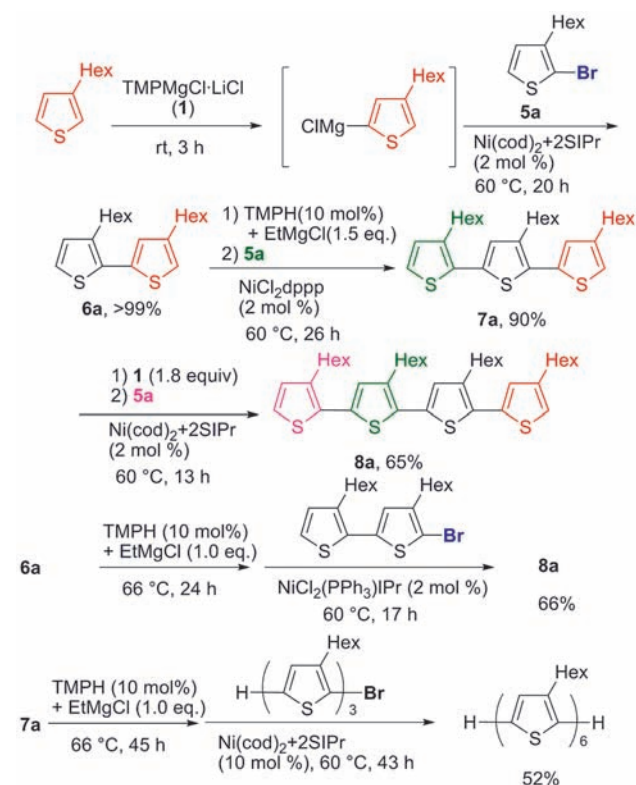
Such a simple iterative extension of the thiophene chain was applied to the short formal syntheses of MK-1 and MK-2, which are organic dye molecules for dye-sensitized organic photovoltaic cells that show excellent energy-conversion efficiency.^{3c–g} As shown in Scheme 4, the reactions of terthiophene **7a** and quaterthiophene **8a** with **1** and subsequent additions of 3-iodo-9-ethylcarbazole in the presence of the palladium catalyst PEPPSI-SIPr¹³ (2.0 mol %) led to incorporation of the carbazole moiety, affording **9a** and **10a**, respectively. The obtained products were identical to the reported intermediates, and subsequent sequential Vilsmeier formylation and Knoevenagel reaction to introduce

Table 1. Regioselective C–H Coupling of **2a** with **5a** To Give **6a** Using Various Transition-Metal Catalysts^a

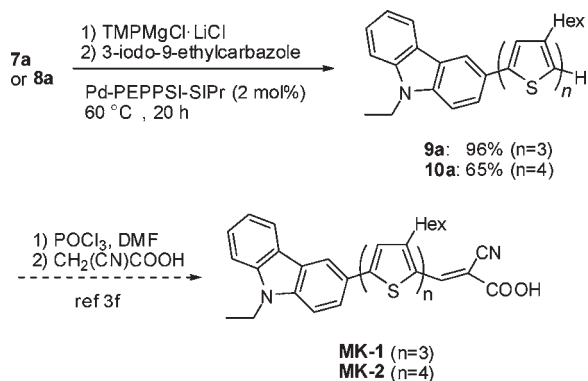
catalyst (mol %)	base (equiv)	temp (°C), time (h) ^b	yield (%)
Pd-PEPPSI-SIPr ^c (2.0)	1 (1.2)	60, 20	74
Pd(P^tBu_3) ₂ (2.0)	1 (1.2)	60, 20	74
$NiCl_2(dppp)$ (2.0)	1 (1.2)	60, 27	52
$NiCl_2(PPh_3)_2$ (2.0)	1 (1.2)	60, 20	8
$Ni(cod)_2/2SIPr$ (2.0)	1 (1.2)	60, 20	>99
$NiCl_2(PPh_3)IPr$ (2.0)	1 (1.2)	60, 20	76
$Ni(cod)_2$ (2.0)	1 (1.2)	60, 20	11
$Ni(cod)_2/2SIPr$ (2.0)	1 (1.2)	rt, 20	88
$Ni(cod)_2/2SIPr$ (2.0)	TMPH (0.1) + $EtMgCl$ (1.0) ^e	60, 20 ^d	77
$NiCl_2(dppp)$ (2.0)	TMPH (0.1) + $EtMgCl$ (1.0) ^e	60, 24 ^d	90
$NiCl_2(dppp)$ (2.0)	Cy_2NH (0.1) + $EtMgCl$ (1.0) ^f	60, 21 ^d	58 ^g

^a Unless otherwise noted, the metalation reaction was carried out with **2a** (0.5 mmol) in THF and stirred at room temperature for 3 h. ^b Reaction conditions for the reaction of **5a** (1.5 equiv). ^c See ref 13. ^d The reaction was carried out with 1.0 equiv of **5a**. ^e Performed at 66 °C for 24 h. ^f Performed at 66 °C for 2 h. ^g A trace amount of head-to-head-type bithiophene was observed by ¹H NMR analysis.

Scheme 3



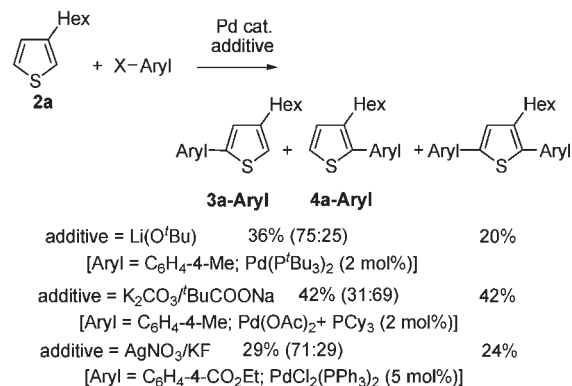
Scheme 4



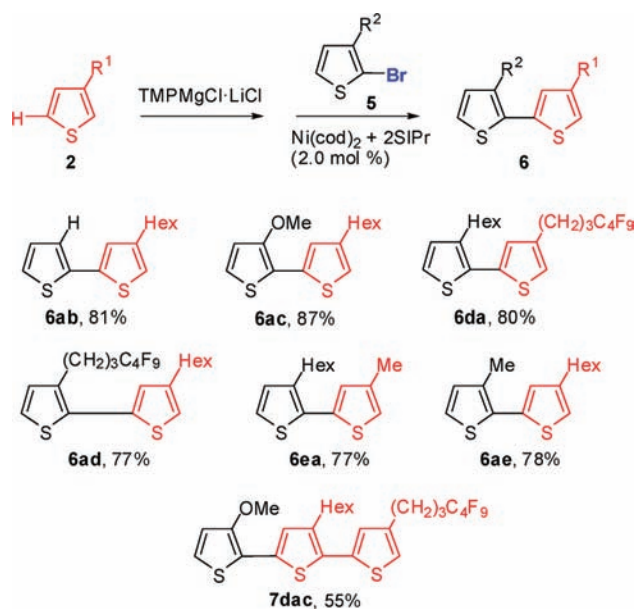
the cyanoacrylic acid moiety on the terminal thiophene ring was performed by the literature method,^{3f} leading to MK-1 and MK-2.

It is noteworthy that the regioselective metalation of 3-substituted thiophene at the C–H bond of the 5-position is applied to the HT connection of thiophene rings. Although metalation of 3-methylthiophene with magnesium amide has also been shown to proceed, further reaction has been focused to date only on the treatment with carbonyl compounds.¹⁴ Selective metalation has been achieved with organolithium or lithium amide^{3f,15} in moderate (9:1) to excellent selectivity at extremely low temperature (−78 °C), but the thus-obtained organolithium has not been employed for the coupling of aryl halides or halothiophenes unless an appropriate metal-exchange protocol with a zinc or magnesium salt is conducted. By contrast, it should be pointed out that the present metalation protocol is carried out at

Scheme 5



Scheme 6



room temperature or slightly higher and that the resulting metalated reaction mixture is directly subjected to further nickel-catalyzed coupling with bromothiophene 5a, leading to HT oligothiophene.

Other reaction systems for C–H functionalization of thiophene derivatives with palladium catalysts did not occur in such a regioselective manner, as shown in Scheme 5. Indeed, when LiO^tBu was employed as the base,¹⁶ arylation with 4-bromotoluene afforded a mixture of 2-arylated 4a-Aryl, 5-arylated 3a-Aryl, and 2,5-diarylated products. A similar trend was observed in the arylation with AgNO₃/KF or K₂CO₃/^tBuCOONa.^{6d,17}

It was also found that different 3-substituted thiophenes could undergo cross-coupling. The reaction proceeded in a similar manner to afford the corresponding bithiophenes 6 in good yields, as summarized in Scheme 6. The reaction of 2a proceeded with unsubstituted 2-bromothiophene (5b), 2-bromo-3-methoxythiophene (5c), a bromothiophene bearing a fluoroalkyl substituent (5d), and 2-bromo-3-methylthiophene (5e). Other 3-substituted thiophenes, including 3-methylthiophene (2b) and a 3-fluoroalkylated thiophene (2d), also reacted with 5a,

leading to **6ba** and **6da**. Bithiophene **6da** was transformed into terthiophene **7dac** in 55% yield by reaction with **5c**.

In summary, we have shown that regiocontrolled metalation of 3-substituted thiophenes using the Knochel–Hauser base **1** or a combination of catalytic TMPH and Grignard reagent as a selective metalating agent allows them to undergo reaction with bromothiophenes to form head-to-tail (HT)-type bithiophenes. By repetition of this reaction, iterative growth of a thiophene unit by single-step extensions was revealed to be operative, leading to HT oligothiophenes, and with this method, a wide variety of oligothiophene derivatives can be synthesized in an extremely facile manner.

■ ASSOCIATED CONTENT

S Supporting Information. Experimental details and characterization of new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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