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Synthesis of thiophene derivatives via palladium-catalyzed coupling reactions

Nobumichi Arai, Takayuki Miyaoku, Shota Teruya, Atsunori Mori *

Department of Chemical Science and Engineering, Kobe University, 1-1 Rokkodai, Nada, Kobe 657-8501, Japan

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Abstract

Thiophene derivatives with multiple substitutions are prepared from vinylidene bromide, which is synthesized by the reaction of thiophene-2-carboxaldehyde with carbon tetrabromide in the presence of PPh_3, as a core molecule through several coupling reactions such as Suzuki–Miyaura coupling and palladium-catalyzed CH arylation. The reactions with a wide variety of organic halides lead to a series of substituted thiophene derivatives in moderate to good yields.

Keywords: Thiophene; Corey–Fuchs reaction; Palladium catalyst; Suzuki–Miyaura coupling; CH arylation

Thiophenes attract considerable attention in advanced materials such as organic TFTs, light emitting devices, and dye-sensitized organic solar cells. A wide variety of thiophene derivatives have revealed to be interesting in spectroscopic properties, electrochemical behaviors, and liquid crystalline characteristics.[1] Development of synthetic protocols for thiophenes, which enable to afford a wide variety of derivatives in a combinatorial manner, has therefore been a major concern in organic synthesis.[2] We herein describe new synthesis of substituted thiophene derivatives with transition metal-catalyzed coupling methodologies, which involve Suzuki–Miyaura coupling[3] and palladium-catalyzed CH arylation.[4]

The starting material for the thiophene derivative is vinylidene bromide **1**, which is readily synthesized from commercially available thiophene-2-carboxaldehyde. Since **1** involves multiple reaction points as shown in Chart 1, synthesis of a wide variety of substituted thiophenes can be performed with transition metal-catalyzed carbon–carbon bond-forming reactions.[5]

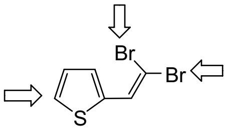
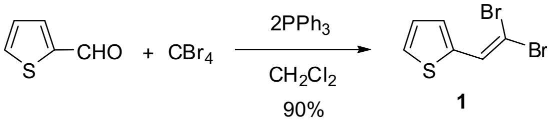


Chart 1.

Synthesis of **1** was carried out by Corey–Fuchs reaction, which is the reaction of thiophene-2-carboxaldehyde with carbon tetrabromide in the presence of PPh_3.[6] The reaction proceeded smoothly to afford **1** in an excellent yield as shown in Scheme 1.

We first envisaged the cross-coupling reaction of **1** at the carbon–bromine bond with several organometallic reagents in the presence of a palladium or nickel catalyst.[7] The reaction of arylmagnesium reagent with **1** has been attempted using a catalytic amount of $Pd(OAc)_2–4PPh_3$ or $NiCl_2$ (dppb) at room temperature to 50 °C to result in giving



Scheme 1.

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[*] Corresponding author. Tel./fax: +81 78 803 6181.
E-mail address: amori@kobe-u.ac.jp (A. Mori).

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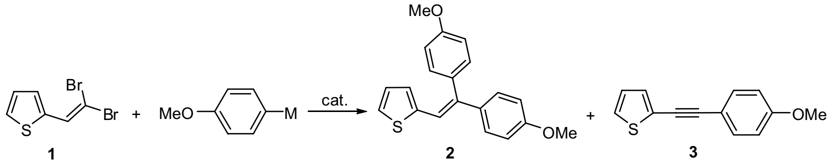
Table 1
Coupling reaction of **1** with an organometallic reagent[a]

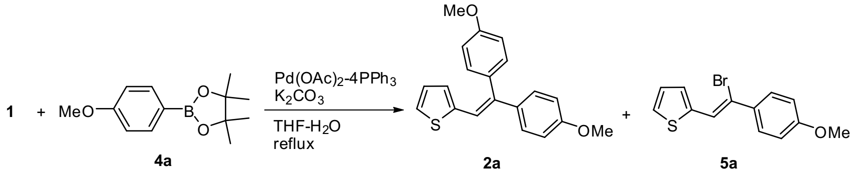


M	Catalyst (mol %)	Solvent	Time (°C)	Time (h)	Yield of **2**	Yield of **3**
MgBr	$Pd(OAc)_2$–4PPh_3 (3)	THF	50	24	0	0
	$NiCl_2$(dppb) (1)	THF	rt	21	0	0
$SnBu_3$[b]	$Pd(dba)_2$ (3)	1,4-Dioxane	50	39	0	48

[a] Unless noted, the reaction was carried out with 2–3 equiv of the organometallic reagent.

[b] As an additive, 2.2 equiv of CsF was added.

Table 2
Suzuki–Miyaura coupling of **1** with boronic acid ester **4**[a]

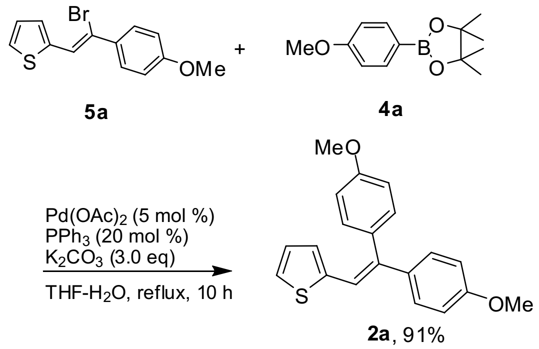


Entry	Boron reagent (equiv)	K_2CO_3 amount (equiv)	Time (h)	Yield (%)	
				2a	**5a**
1	1.0	3.0	18	0	47
2	2.2	3.0	11	0	80
3	3.0	6.0	24	>99	0

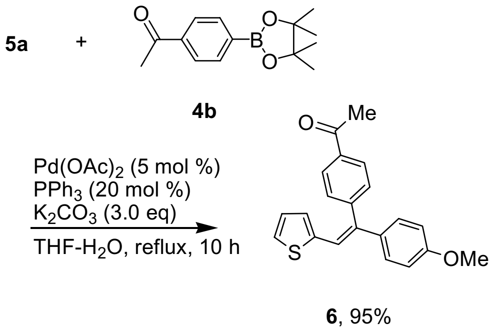
[a] The reaction was carried out with 5 mol % of the palladium catalyst in THF–H_2O.

unidentified products and no desired coupling product **2** was obtained. Migita–Kosugi–Stille coupling with arylstannane also afforded undesired products.[8] Although the reaction proceeded under certain conditions, the major product was found to be the disubstituted alkyne **3**, which would be obtained by the coupling reaction and following dehydrobromination or vice versa. The results are summarized in Table 1.

By contrast, it was found that the Suzuki–Miyaura coupling with arylboronic acid esters as an organometallic reagent afforded the desired coupling product in a reasonable yield.[3] As summarized in Table 2, the reaction of **1** with 3 mol amounts of arylboronate **4a** in the presence of aqueous potassium carbonate under reflux conditions for 24 h afforded the desired coupling product **2a** in a quantitative yield. On the other hand, reducing the amount of potassium carbonate and the boron reagent furnished the mono-substituted product **5a**. It was found that mono/bis-substitution was controllable by the employed amount of potassium carbonate. Even with 2.2 mol amounts of **4a**, mono-substituted product **5a** was obtained in 80% yield in the presence of 3 mol amounts of potassium carbonate. It seems to react smoothly when THF–H_2O is employed as the solvent system, which would avoid undesired elimination to alkyne in the presence of a base. Although the use of an organic solvent such as toluene, ethanol, and DME

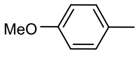
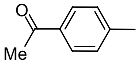
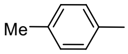
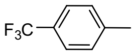
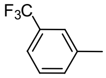
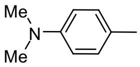


Scheme 2.

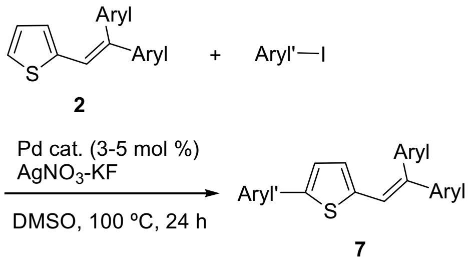


Scheme 3.

Table 3
Coupling reaction of **1** with arylboronates[a]

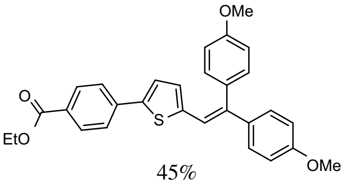
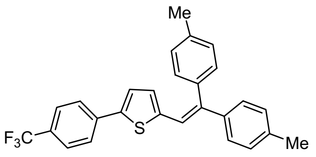
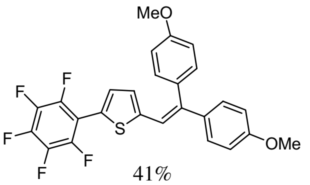
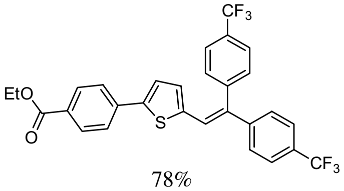
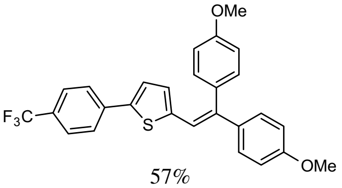
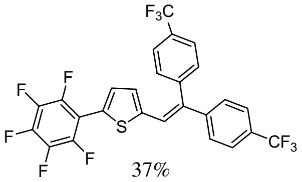
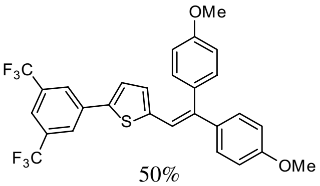
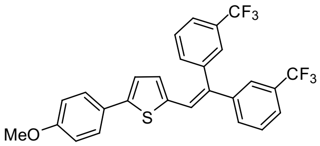
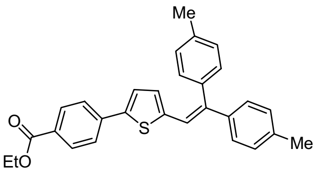
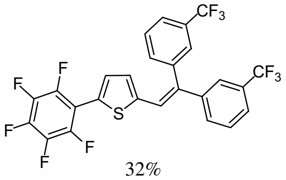
Entry	Aryl (equiv)	Time (h)	Yield (%)
1	 **4a** (3)	24	>99
2	 **4b** (3)	24	>99
3	 **4c** (2.4)	46	90
4	 **4d** (2.2)	45	83
5	 **4e** (3)	24	>99
6	 **4f** (2.4)	45	91

[a] The reaction was carried out under the similar conditions to those for the entry 3 of Table 2.



Scheme 4.

Table 4
Palladium-catalyzed CH arylation of thiophene derivative **2**

Product (yield)	Product (yield)
 45%	 80%
 41%	 78%
 57%	 37%
 50%	 26%
 86%	 32%

[a] The reaction was carried out with **2** (0.3 mmol) and aryl iodide (0.36 mmol) in DMSO (1.8 mL) under nitrogen atmosphere with $PdCl_2(PPh_3)_2$ (5 mol %) or $PdCl_2(dppb)$ (3 mol %).

was preliminary examined, the reactions were found to be unsuccessful to result in no reaction or in giving a mixture of **2**, **3**, and **5**.

The finding that mono-substituted product **5** has been selectively obtained under a certain condition enables the coupling reaction to synthesize differently-substituted thiophene derivatives in a facile manner. When **5a** was treated with **4a** in the presence of a palladium catalyst and potassium carbonate, disubstituted **2a** was obtained in an excellent yield (Scheme 2). However, treatment of arylstannane instead of **4a** afforded the internal alkyne **3a** as a major product, while disubstituted **2a** was not obtained at all. The reaction with the other arylboronate **4b** also proceeded smoothly to afford the differently substituted **6** in 95% yield (Scheme 3).

The disubstituted thiophene derivatives **2** were synthesized in a similar manner. As shown in Table 3, various boron reagents **4** were employed for the reaction to obtain thiophene derivatives bearing electron-donating or electron-withdrawing substituents in excellent yields under similar conditions to the synthesis of **2a**.

The thiophene derivatives **2** were then subjected to the functionalization at the 5-position of the thiophene ring with the palladium-catalyzed CH arylation reaction in the presence of $AgNO_3$/KF as an activator (Scheme 4).[2b] Table 4 summarizes the results. The products bearing a variety of substituents **7** were obtained in moderate to good yields. The reaction with an aryl halide bearing an electron-withdrawing substituent proceeded in a relatively higher yield than that bearing electron-donating group. The reaction of **6** bearing different aryl groups as substituents has also been attempted and found that CH arylation reaction took place. However, scrambling of the stereochemistry of the double bond was observed to some extent under the conditions shown in Table 4. Further studies would be required to undergo the reaction with retention of the stereochemistry.

In summary, we have demonstrated the preparation of multiple substituted thiophene derivatives starting from vinylidene bromide **1** using Suzuki–Miyaura coupling and the palladium-catalyzed CH arylation strategies. The method allowed to synthesize a variety of trisubstituted thiophene derivatives **7** in a combinatorial manner. These molecules exhibited extended π-conjugation. Further studies on the properties of the thiophene derivative **6** leading to find the utility of these molecules as advanced materials are under way.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.12.010.

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