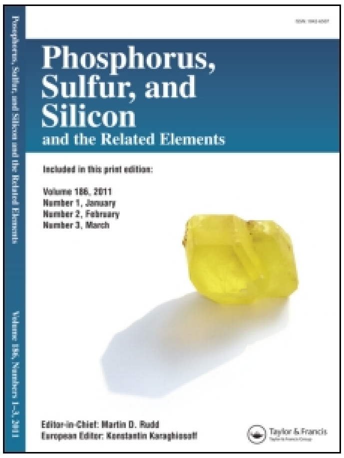

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A Convenient Synthesis of 3,3-Bis(thienyl)propionic Acids by Platinum (II)-Catalyzed Reaction of Thiophenes with Propiolic Acids

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A CONVENIENT SYNTHESIS OF 3,3-BIS(THIENYL)PROPIONIC ACIDS BY PLATINUM (II)-CATALYZED REACTION OF THIOPHENES WITH PROPIOLIC ACIDS

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Platinum(II)-catalyzed hydroarylation of propiolic acids was applied to thiophenes, and we found that the reaction with thiophenes predominantly afforded double thienylated products. Reaction of thiophenes with ethyl propiolate proceeded efficiently in the presence of K_2PtCl_4 (2 mol%) and AgOTf (8 mol%) in trifluoroacetic acid under mild conditions to give ethyl 3,3-bis(substituted thienyl)propionates in good yields. The same platinum(II)-catalyzed reaction with propiolic acid instead of the ethyl ester provided bis(substituted thienyl)propionic acids in high yields.

Keywords Hydroarylation; platinum catalyst; propiolic acids; thiophenes

INTRODUCTION

Functionalization of C–H bonds in hydrocarbons is one of the most important topics in organic synthesis because C–H bonds are stable and less reactive.[1] Hydroarylation of alkynes is a useful method for functionalization of aromatic C–H bonds with alkynes and provides a direct process for preparing arylated olefins from aromatics and alkynes. Aromatic substrates are abundant hydrocarbons in nature and can be used as starting materials in this process. Furthermore, this direct process reduces the total number of reaction steps, leading to an economical process. Therefore, the application to sulfur compounds, that is, thiophenes, is significant and attracts much attention.

Previously, we reported Pd(II)-catalyzed hydroarylation of alkynes with arenes.[2] In this reaction, $Pd(OAc)_2$ catalyzes this hydroarylation in trifluoroacetic acid (TFA) under mild conditions (Scheme 1). Relatively electron-rich aromatics provide arylated *cis*-olefins. The use of TFA is essential. TFA activates both the reactivity of the Pd catalyst and the final

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Dedicated to Professor Naomichi Furukawa on the occasion of his 70th birthday.

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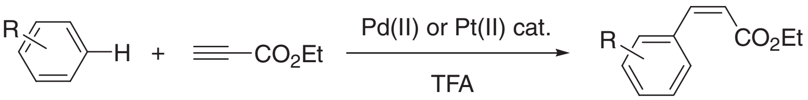
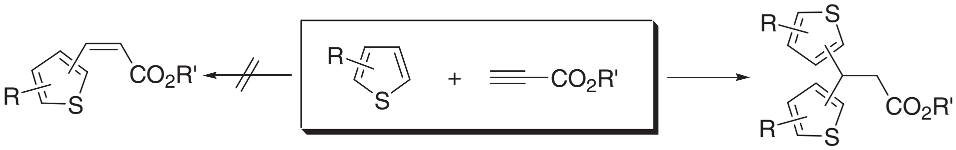


Scheme 1

protonation step. In the $Pd(OAc)_2$-catalyzed hydroarylation of ethyl propiolate, however, a butadiene derivative is formed as a byproduct, together with the desired ethyl cinnamate. The formation of this butadiene derivative reduces the yield of the cinnamate. To increase the selectivity, we examined the use of platinum chloride as the catalyst.[3] The addition of the $PtCl_2$/AgOTf catalyst instead of $Pd(OAc)_2$ led to an absence of butadiene derivatives. This $PtCl_2$/AgOTf-catalyzed hydroarylation of ethyl propiolate using other electron-rich arenes proceeded very well. Furthermore, K_2PtCl_4/AgOTf was effective for hydroarylation. The desired products were obtained in higher yield. The K_2PtCl_4/AgOTf catalyst was effective in the reaction of propiolic acid with benzene and gave a higher yield of cinnamic acid than did the $PtCl_2$/AgOTf catalyst.

During the course of our study on hydroarylation, we applied the K_2PtCl_4/AgOTf-catalyzed reaction to sulfur compounds to broaden the scope of our hydroarylation reaction. Although there are a few reports of the metal-catalyzed reaction of thiophenes with alkynes (thienylation of alkynes),[4] only one article has reported the double thienylation of alkynes that is catalyzed by indium triflate.[4a] The indium triflate–catalyzed thienylation, however, requires severe reaction conditions: 130°C and 60 h for the reaction of 2-ethylthiophene with phenylacetylene and 90°C and 50 h for the reaction of 2,5-dimethylthiophene with ethyl propiolate. Interestingly, the reaction of thiophenes with ethyl propiolate catalyzed by a K_2PtCl_4/AgOTf catalyst did not give the desired thienylacrylate, but instead afforded the double thienylated product under very mild conditions, as shown in Scheme 2. In this article we report in detail the Pt(II)-catalyzed double thienylation of ethyl propiolate and propiolic acid affording bis(substituted thienyl)propionic acids and ethyl esters, respectively.

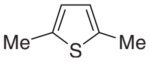
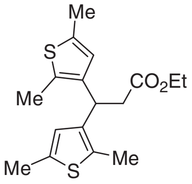
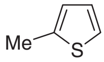
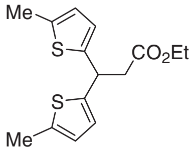
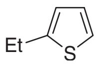
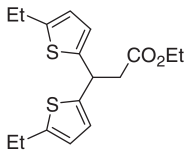
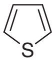
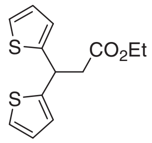
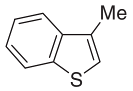
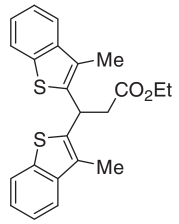


Scheme 2

RESULTS AND DISCUSSION

First, we chose 2,5-dimethylthiophene as a substrate because we expected that the three position was the only reactive site, and a simple and easily assignable product was formed. When a solution of 2,5-dimethylthiophene (**1a**) and ethyl propiolate (**2a**) in TFA was reacted in the presence of K_2PtCl_4 (2 mol%) and AgOTf (8 mol%) at 40°C for 6 h, ethyl 3,3-bis(2,5-dimethylthien-3-yl)propionate (**3a**) was isolated in 46% yield by column chromatography on silica gel after workup of the reaction mixture (Table I, entry 1). Using 2 mL of TFA, product **3a** was obtained in 50% yield (entry 2). Further increasing the amount

Table I Reaction of ethyl propiolate (**2a**) with thiophenes **1**[a]

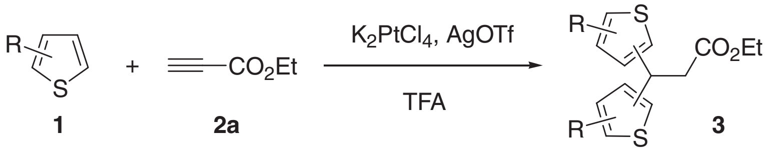
Entry	Thiophene	**1** (mmol)	**2a** (mmol)	TFA (mL)	Temp (°C)	Time (h)	Product	Yield (%)[b]
1	 **1a**	2	1	1	40	6	**3a** 	46
2	**1a**	2	1	2	40	6	**3a**	50
3	**1a**	2	1	4	40	6	**3a**	42
4	**1a**	1.5	1.5	2	40	6	**3a**	63
5	 **1b**	4	2	2	r.t.	2	**3b** 	35
6	 **1c**	4	2	2	r.t.	2	**3c** 	46
7	 **1d**	3	1	2	40	24	**3d** 	63
8	 **1e**	4	2	1	40	45	**3e** 	53

[a] Reaction conditions: K_2PtCl_4 (0.02 mmol), AgOTf (0.08 mmol), **1**, **2a**, and TFA.

[b] Isolated yield based on the least amount of substrates.

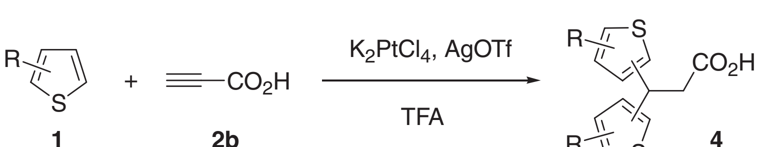
of TFA to 4 mL, however, did not improve the yield (entry 3). Finally, the best result, a 63% yield, was obtained using 1.5 mmol each of **1a** and **2a** (entry 4). No monothienylated products were obtained in the present reaction. This result suggests that double thienylation occurs efficiently, even in the case of an equimolar amount of the reactants.

We then examined the reaction of 2-methylthiophene (**1b**) with ethyl propiolate. Similarly, double thienylation of **1b** occurred, giving ethyl 3,3-bis(5-methylthien-2-yl)propionate (**3b**) in 35% yield (Table I, entry 5). The reaction of 2-ethylthiophene (**1c**) with **2a** yielded ethyl 3,3-bis(5-ethylthien-2-yl)propionate (**3c**) as the sole identified product (entry 6). In the case of thiophene (**1d**), an excess amount of **1d** was required to get a reasonable result. The reaction of **2** using three equivalents of **1d** gave ethyl 3,3-bis(thien-2-yl)propionate (**3d**) in 63% yield. In the reaction of 3-methylbenzothiophene (**1e**) with **2a**, the reactivity was very low. The reaction of **1e** with **2** required a longer reaction time, 45 h, at 40°C to obtain a reasonable yield. A twofold addition of **1e** occurred to give ethyl 3,3-bis(3-methylbenzo[b]thien-2-yl)propionate (**3e**) in 53% yield (entry 8). Interestingly, the double thienylation products were obtained predominantly. The outline of the above reactions is drawn in Scheme 3.



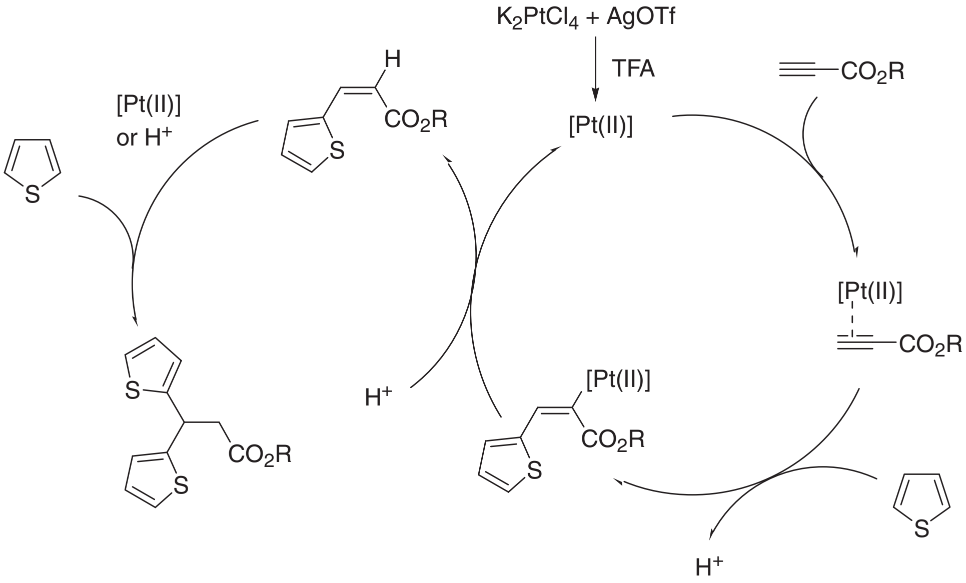
Scheme 3

When the reaction of **1a** with **2a** was conducted for a longer time, it was found that product **3a** was in part hydrolyzed to yield the corresponding acid, 3,3-bis(2,5-dimethylthien-3-yl)propionic acid (**4a**). Thus, we examined the reaction of thiophenes **1** with propiolic acid (**2b**) in TFA at 40°C (Scheme 4). The results are given in Table II. When the reaction of **1a** (3 mmol) with **2b** (1 mmol) was carried out in TFA (2 mL) for 15 h, double thienylated propionic acid **4a** was formed in 91% yield (Table II, entry 1). The similar reaction of 2-methylthiophene (**1b**) for 48 h gave 3,3-bis(5-methylthien-2-yl)propionic acid (**4b**) in 60% yield (entry 2). In the case of **1c**, the reaction of **1c** (2 mmol) with **2b** (1 mmol) was conducted in a mixed solvent of TFA (1 mL) and AcOH (1 mL) to give 3,3-bis(5-ethylthien-2-yl)propionic acid (**4c**) in 90% yield (entry 3). The reaction of **1d** (3 mmol) with **2b** (1 mmol) in TFA (2 mL) for 72 h afforded 3,3-bis(2-thienyl)propionic acid (**4d**) in 51% yield (entry 4).



Scheme 4

The double thienylation reaction is thought to occur stepwise, as shown in Scheme 5. First, a cationic platinum catalyst is formed by interaction of K_2PtCl_4 with AgOTf in TFA and then coordinates with the triple bond in ethyl propiolate or propiolic acid. Next, thiophene attacks the resulting electron-deficient triple bond to yield a vinyl platinum complex, which is immediately protonated by TFA to produce a thienylacrylate or acrylic acid. The thienylacrylate is activated by the cationic platinum catalyst or an acid. Again,



Scheme 5

a thiophene reacts with this complex. Finally, protonation affords the double thienylated product.

In conclusion, we have developed an efficient synthesis of bis(thienyl)propiolic acid derivatives by a one-pot reaction. This synthesis involves a double thienylation reaction of propiolic acids in a K_2PtCl_4/AgOTf catalytic system. The double thienylation reaction is rationalized by hydroarylation of propiolic acids with thiophenes and the subsequent thienylation reaction. This catalytic reaction is effective for synthesis of 3,3-bis(substituted thienyl)propionic acid derivatives.

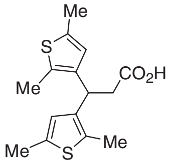
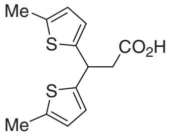
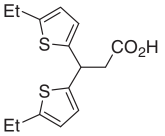
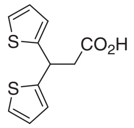
EXPERIMENTAL

All solvents and reagents were commercially available and used as received without further purification. All reactions were conducted in a dry Pyrex tube with a rubber septum. ^1H and ^{13}C NMR spectra were recorded on a JEOL JNM-AL 300 FT-NMR (300 MHz) system using TMS as internal standard. Melting points were measured with a Yanaco micro melting apparatus and were uncorrected. Column chromatographic separations were carried out using silica gel as the stationary phase. Precoated plates (silica gel 60 F_{254}, Merck, on aluminum sheets) were used for TLC analysis. Elemental analysis was performed by the Service Center of the Elementary Analysis of Organic Compounds, Faculty of Science, Kyushu University.

General Procedure for Reaction of Thiophenes 1 with Ethyl Propiolate (2a) or Propiolic Acid (2b)

After a mixture of K_2PtCl_4 (0.02 mmol) and AgOTf (0.08 mmol) in TFA (2 mL) was stirred at room temperature for 10 min, a thiophene and **2** were added, and the mixture was stirred at the desired temperature. After the reaction, the mixture was poured into water (20 mL), neutralized with $NaHCO_3$, and extracted with CH_2Cl_2 (20 mL × 3). The

Table II Reaction of propiolic acid (2b) with thiophenes 2[a]

Entry	**1** (mmol)	**2b** (mmol)	TFA (mL)	Time (h)	Product	Yield (%)[b]
1	**1a** 3	1	2	15	**4a** 	91
2	**1b** 4	1	2	48	**4b** 	60
3	**1c** 2	1	1 AcOH (1 mL)	48	**4c** 	90
4	**1d** 3	1	2	72	**4d** 	51

[a] Reaction conditions: K_2PtCl_4 (0.02 mmol), AgOTf (0.08 mmol), **1**, **2b**, and TFA at 40°C.

[b] Isolated yield based on the least amount of substrates.

combined organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel using a mixture of ethyl acetate and hexane as eluent.

Ethyl 3,3-bis(2,5-dimethylthien-3-yl)propionate (3a). Mp 58–60°C; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.13 (t, $J = 7.2$ Hz, 3 H, Me), 2.32 (s, 6 H, Me), 2.36 (s, 6 H, Me), 2.82 (d, $J = 7.8$ Hz, 2 H, CH_2), 4.03 (q, $J = 7.2$ Hz, 2 H, CH_2), 4.42 (t, $J = 7.8$ Hz, 1 H, CH), 6.52 (s, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.8, 13.9, 15.1, 34.0, 41.2, 60.2, 124.5, 130.4, 135.2, 138.1, 171.6. Anal. Calcd for $C_{17}H_{22}O_2S_2$: C, 63.32; H, 6.88. Found: C, 63.35; H, 6.88.

Ethyl 3,3-bis(5-methylthien-2-yl)propionate (3b). Oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.18 (t, $J = 7.2$ Hz, 3 H, Me), 2.40 (s, 6 H, Me), 3.01 (d, $J = 7.7$ Hz, 2 H, CH_2), 4.09 (q, $J = 7.2$ Hz, 2 H, CH_2), 4.86 (t, $J = 7.7$ Hz, 1 H, CH), 6.52–6.54 (m, 2 H, ArH), 6.66–6.67 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 15.2, 38.4, 43.1, 60.6, 123.9, 124.5, 138.5, 144.6, 171.0. This compound was further confirmed by acid hydrolysis to the corresponding acid **4b**.

Ethyl 3,3-bis(5-ethylthien-2-yl)propionate (3c). Oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.17 (t, $J = 7.2$ Hz, 3 H, Me), 1.26 (t, $J = 7.5$ Hz, 6 H, Me), 2.77 (q, $J = 7.5$ Hz, 4 H, CH_2), 3.02 (d, $J = 7.8$ Hz, 2 H, CH_2), 4.09 (q, $J = 7.2$ Hz, 2 H, CH_2), 4.88 (t, $J = 7.8$ Hz, 1 H, CH), 6.56–6.57 (m, 2 H, ArH), 6.68–6.69 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 15.7, 23.4, 38.5, 43.3, 60.6, 122.6, 123.7, 144.2, 146.2, 171.0. This compound was further confirmed by acid hydrolysis to the corresponding acid **4c**.

Ethyl 3,3-bis(thien-2-yl)propionate (3d). Oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.10 (t, $J = 7.2$ Hz, 3H, Me), 3.03 (d, $J = 7.5$ Hz, 2 H, CH_2), 4.02 (q, $J = 7.2$ H, CH_2), 4.99 (t, $J = 7.5$ Hz, CH), 6.84–6.86 (m, 4 H, ArH), 7.09–7.11 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 14.1, 38.1, 43.5, 60.7, 124.2, 124.4, 126.6, 146.8, 170.8. This compound was further confirmed by acid hydrolysis to the corresponding acid **4d**.

Ethyl 3,3-bis(3-methylbenzo[b]thien-2-yl)propionate (3e). Mp 220–222°C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.11 (t, $J = 7.2$ Hz, 3 H, Me), 2.42 (s, 6 H, Me), 3.18 (d, $J = 7.5$ Hz, 2 H, CH_2), 4.04 (q, $J = 7.2$ Hz, 2 H, CH_2), 5.49 (t, $J = 7.5$ Hz, 1 H, CH), 7.23–7.33 (m, 4 H, ArH), 7.59 (d, $J = 7.8$ Hz, 2 H, ArH), 7.71 (d, $J = 8.1$ Hz, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 11.9, 14.0, 35.3, 42.4, 60.8, 121.6, 122.3, 123.9, 124.0, 127.7, 138.2, 140.1, 140.4, 170.7. Calcd for $C_{23}H_{22}O_2S_2$: C, 70.02; H, 5.62. Found: C, 70.39; H, 5.54.

3,3-Bis(2,5-dimethylthien-3-yl)propionic acid (4a). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.30 (s, 6 H, Me), 2.36 (s, 6 H, Me), 2.86 (d, $J = 7.8$ Hz, 2 H, CH_2), 4.41 (t, $J = 7.8$ Hz, 1 H, CH), 6.50 (s, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 12.9, 15.3, 33.8, 40.9, 124.5, 130.8, 135.6, 137.9, 177.3. Calcd for $C_{15}H_{18}O_2S_2$: C, 61.19; H, 6.16. Found: C, 61.46; H, 6.18.

3,3-Bis(5-methylthien-2-yl)propionic acid (4b). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.34 (s, 6 H, Me), 3.00 (d, $J = 7.8$ Hz, 2 H, CH_2), 4.77 (t, $J = 7.8$ Hz, 1 H, CH), 6.47–6.48 (m, 2 H, ArH), 6.60–6.61 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.3, 38.0, 42.7, 124.0, 124.6, 138.8, 144.3, 177.0. Calcd for $C_{13}H_{14}O_2S_2$: C, 58.62; H, 5.30. Found: C, 58.76; H, 5.37

3,3-Bis(5-ethylthien-2-yl)propionic acid (4c). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.18 (t, $J = 7.5$ Hz, 6 H, Me), 2.69 (q, $J = 7.5$ Hz, 4 H, CH_2), 3.00 (d, $J = 7.8$ Hz, 2 H, CH_2), 4.79 (t, $J = 7.8$ Hz, 1 H, CH), 6.48–6.50 (m, 2 H, ArH), 6.61–6.63 (m, 2 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 15.6, 23.4, 38.0, 42.9, 122.6, 123.7, 143.9, 146.4, 177.1. Calcd for $C_{15}H_{18}O_2S_2$: C, 61.19; H, 6.16. Found: C, 61.46; H, 6.21.

3,3-Bis(2-thienyl)propionic acid (4d). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 3.16 (d, $J = 7.7$ Hz, 2 H, CH_2), 5.05 (t, $J = 7.7$ Hz, 1 H, CH), 6.92–6.94 (m, 4 H, ArH), 7.17–7.19 (m, 4 H, ArH); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 37.6, 43.0, 124.3, 124.4, 126.7, 146.5, 176.1. Calcd for $C_{11}H_{10}O_2S_2$: C, 55.44; H, 4.23. Found: C, 55.64; H, 4.36.

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