Double Thienylation of Alkynes in the Platinum(II)-catalyzed Reaction of Thiophenes with Propiolic Acids

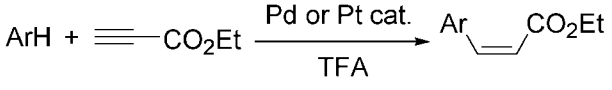
Mory Laye Keita, Tomohiro Mizuhara, Juzo Oyamada, and Tsugio Kitamura*
Department of Chemistry and Applied Chemistry, Faculty of Engineering, Saga University, Honjo-machi, Saga 840-8502

(Received June 22, 2007; CL-070673; E-mail: kitamura@cc.saga-u.ac.jp))

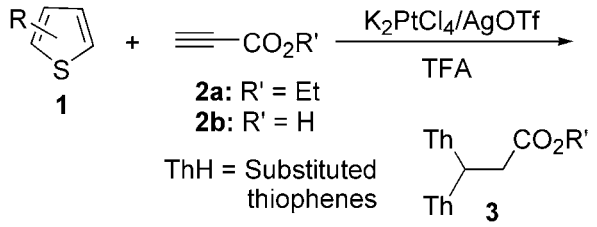
Platinum-catalyzed hydroarylation of alkynes was applied to thiophenes. Reaction of thiophenes with ethyl propiolate in trifluoroacetic acid in the presence of a K_2PtCl_4/AgOTf catalyst gave bis(substituted thienyl)propionates in good yields. The same Pt-catalyzed reaction with propiolic acid proceeded efficiently to provide bis(substituted thienyl)propionic acids in high yields.

Previously, we reported Pd^{II}-catalyzed hydroarylation of alkynes with arenes.[1] 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 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.[2] The addition of the $PtCl_2$/AgOTf catalyst instead of $Pd(OAc)_2$ led to produce no 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 a 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 examined a K_2PtCl_4/AgOTf-catalyzed reaction of thiophenes with ethyl propiolate to broaden the scope of our hydroarylation reaction. Interestingly, some dithienylalkanoic acid derivatives show biological activities such as herbicides,[3] antagonists of M3 muscarinic receptors,[4] antispasmodics,[5] and analgesics.[6] Therefore, it is significant to explore a simple and convenient method for preparing such dithienylalkanoic acid derivatives. However, there are only a few reports of the metal-catalyzed reaction of thiophenes with alkynes (thienylation of alkynes).[7] Only one paper reports the double thienylation of alkynes catalyzed by indium triflate.[7a] Indium triflate-catalyzed thienylation 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 K_2PtCl_4/AgOTf-catalyzed reaction



Scheme 1.



Scheme 2.

of thiophenes with ethyl propiolate did not give the desired thienylacrylate, but instead afforded the double thienylated product *under very mild conditions*, as shown in Scheme 2. Here, we report a new Pt^{II}-catalyzed double thienylation of ethyl propiolate.

First, we chose 2,5-dimethylthiophene as a substrate because we expected that the 3 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 allowed to react in the presence of K_2PtCl_4 (2%) and AgOTf (8%) at 40 °C for 6 h, ethyl 3,3-bis(2,5-dimethylthien-3-yl)propionate (**3a**)[8] was isolated in 46% yield by column chromatography on silica gel after work-up of the reaction mixture (Table 1, Entry 1). Using 2 mL of TFA, product **3a** was obtained in 50% yield (Entry 2). Further increasing the amount 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 mono-thienylated 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.

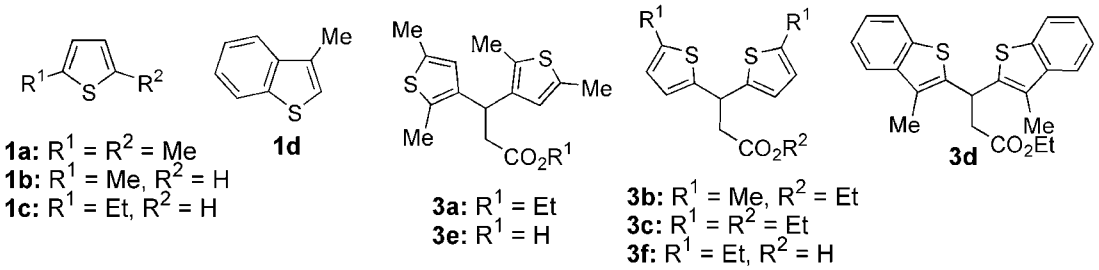
We then examined the K_2PtCl_4/AgOTf-catalyzed reaction of 2-methylthiophene (**1b**) with **2a**. Similarly, double thienylation of **1b** occurred, giving ethyl 3,3-bis(5-methylthien-2-yl)propionate (**3b**)[8] in 35% yield (Entry 5). The reaction of 2-ethylthiophene (**1c**) with **2a** yielded ethyl 3,3-bis(5-ethylthien-2-yl)propionate (**3c**)[8] as the sole identified product (Entry 6). In the reaction of 3-methylbenzothiophene (**1d**) with **2a**, the reactivity was very low. The reaction of **1d** with **2a** required a longer reaction time, 45 h, at 40 °C to obtain a reasonable yield. Doubling the addition of **1d** gave ethyl 3,3-bis(3-methylbenzo[*b*]thien-2-yl)propionate (**3d**)[8] in 53% yield (Entry 7). Interestingly, the double thienylation products were obtained predominantly.

When the reaction of **1a** with **2a** was conducted for a longer time, product **3a** was hydrolyzed to yield the corresponding acid. The reaction of thiophenes with propiolic acid (**2b**) was then examined. A similar reaction of **1a** (3 mmol) with **2b** (1 mmol) was conducted in TFA (2 mL) at 40 °C for 15 h (Entry 8). We obtained 3,3-bis(2,5-dimethylthien-3-yl)propionic acid (**3e**)[8] in 91% yield. In the reaction of **1c** (2 mmol) with **2b** (1 mmol),

Table 1. Double thienylation of **2** catalyzed by a platinum catalyst[a]

Entry	**1**/mmol	**2**/mmol	TFA/mL	Time/h	Product	Yield[b]/%
1	2 (**1a**)	1 (**2a**)	1	6	**3a**	46
2	2 (**1a**)	1 (**2a**)	2	6	**3a**	50
3	2 (**1a**)	1 (**2a**)	4	6	**3a**	42
4	1.5 (**1a**)	1.5 (**2a**)	2	6	**3a**	63
5[c]	1 (**1b**)	1 (**2a**)	2	2	**3b**	35
6[c]	1 (**1c**)	1 (**2a**)	2	2	**3c**	46
7	1 (**1d**)	1 (**2a**)	1	45	**3d**	53
8	3 (**1a**)	1 (**2b**)	2	15	**3e**	91
9	2 (**1c**)	1 (**2b**)	2	48	**3f**	90

[a]Reaction conditions: K_2PtCl_4 (0.02 mmol), AgOTf (0.08 mmol), **1**, **2**, and TFA at 40 °C. [b]Isolated yield based on the least amount of substrates. [c]Reaction was conducted at room temperature.



3,3-bis(5-ethylthien-2-yl)propionic acid (**3f**)[8] was also isolated in 90% yield (Entry 9).

The double thienylation reaction is thought to occur stepwise, as follows.[9] First, a cationic platinum catalyst coordinates with the triple bond in ethyl propiolate or propiolic acid. Then, 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. A cationic platinum catalyst activates the thienylacrylate or acid by coordination. Again, a thiophene reacts with this complex. Finally, protonation affords the double-thienylated product. The second addition of the thiophene was confirmed by the reaction of 3-(2-thienyl)acrylic acid with thiophene, which gave 3,3-bis(2-thienyl)propionic acid in a moderate yield.

In summary, we demonstrated an efficient double thienylation of propiolate or propiolic acid catalyzed by a K_2PtCl_4/AgOTf system. The hydroarylation of ethyl propiolate or propiolic acid with thiophenes proceeds effectively by using K_2PtCl_4/AgOTf catalyst. The subsequent thienylation reaction occurs immediately to afford the double-thienylated products in good to high yields. Further development using this catalytic system is in progress.

This work was supported by a Grant-in-Aid for Scientific Research on Priority Areas "Advanced Molecular Transformations of Carbon Resources" from the Ministry of Education, Culture, Sports, Science and Technology, Japan. J. O. thanks JSPS Research Fellowships for Young Scientists.

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8 **3a**: mp 58–60 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.13 (t, J = 7.2 Hz, 3H, Me), 2.32 (s, 6H, Me), 2.36 (s, 6H, Me), 2.82 (d, J = 7.8 Hz, 2H, CH_2), 4.03 (q, J = 7.2 Hz, 2H, CH_2), 4.42 (t, J = 7.8 Hz, 1H, CH), 6.52 (s, 2H, ArH). **3b**: oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (t, J = 7.2 Hz, 3H, Me), 2.40 (s, 6H, Me), 3.01 (d, J = 7.7 Hz, 2H, CH_2), 4.09 (q, J = 7.2 Hz, 2H, CH_2), 4.86 (t, J = 7.7 Hz, 1H, CH), 6.52–6.54 (m, 2H, ArH), 6.66 (d, J = 3.3 Hz, 2H, ArH). **3c**: oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.17 (t, J = 7.2 Hz, 3H, Me), 1.26 (t, J = 7.5 Hz, 6H, Me), 2.77 (q, J = 7.5 Hz, 4H, CH_2), 3.02 (d, J = 7.8 Hz, 2H, CH_2), 4.09 (q, J = 7.2 Hz, 2H, CH_2), 4.88 (t, J = 7.8 Hz, 1H, CH), 6.56–6.57 (m, 2H, ArH), 6.68 (d, J = 3.6 Hz, 2H, ArH). **3d**: mp 220–222 °C. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.11 (t, J = 7.2 Hz, 3H, Me), 2.42 (s, 6H, Me), 3.18 (d, J = 7.5 Hz, 2H, CH_2), 4.04 (q, J = 7.2 Hz, 2H, CH_2), 5.49 (t, J = 7.5 Hz, 1H, CH), 7.21–7.33 (m, 4H, ArH), 7.59 (d, J = 7.8 Hz, 2H, ArH), 7.71 (d, J = 8.1 Hz, 2H, ArH). **3e**: oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.30 (s, 6H, Me), 2.36 (s, 6H, Me), 2.86 (d, J = 7.8 Hz, 2H, CH_2), 4.41 (t, J = 7.8 Hz, 1H, CH), 6.50 (s, 2H, ArH). **3f**: oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 1.18 (t, J = 7.5 Hz, 6H, Me), 2.69 (q, J = 7.5 Hz, 4H, CH_2), 3.00 (d, J = 7.8 Hz, 2H, CH_2), 4.79 (t, J = 7.8 Hz, 1H, CH), 6.48–6.50 (m, 2H, ArH), 6.62 (d, J = 3.3 Hz, 2H, ArH).

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Published on the web (Advance View) August 11, 2007; doi:10.1246/cl.2007.1150