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Palladium-Catalyzed Perarylation of 3-Thiophene- and 3-Furancarboxylic Acids Accompanied by C−H Bond Cleavage and Decarboxylation

Masaya Nakano, Hayato Tsurugi, Tetsuya Satoh, and Masahiro Miura*

Department of Applied Chemistry, Faculty of Engineering, Osaka University, Suita, Osaka 565-0871, Japan

miura@chem.eng.osaka-u.ac.jp

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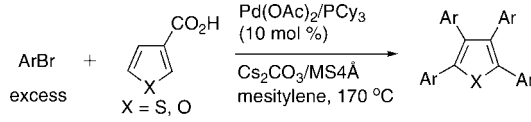
ABSTRACT



3-Thiophene- and 3-furancarboxylic acids efficiently undergo perarylation accompanied by cleavage of the three C−H bonds and decarboxylation upon treatment with excess aryl bromides in the presence of a palladium catalyst to give the corresponding tetraarylated products in good yields.

Poly- and oligoaryl compounds involving a thiophene unit have recently attracted much attention due to their useful electronic and optical properties.[1] One of the most practical methods to prepare such arylated heteroarenes is the palladium-catalyzed cross-coupling of aryl halides with heteroarylmetals or of heteroaryl halides with arylmetals.[2] It is also known that a number of five-membered heteroarenes including thiophenes and furans can couple with aryl halides directly at their 2- and 5-positions under the influence of palladium catalysts.[3]

Meanwhile, catalytic reactions via cleavage of C−H[3,4] and C−C[5] bonds have attracted much attention from atom-economic and chemoselective points of view, and various catalytic processes involving different modes to activate the relatively inert bonds have been developed.

While the above direct arylation of heteroarenes is a useful example, among the most promising and general activation strategies is to utilize the proximate effect by coordination

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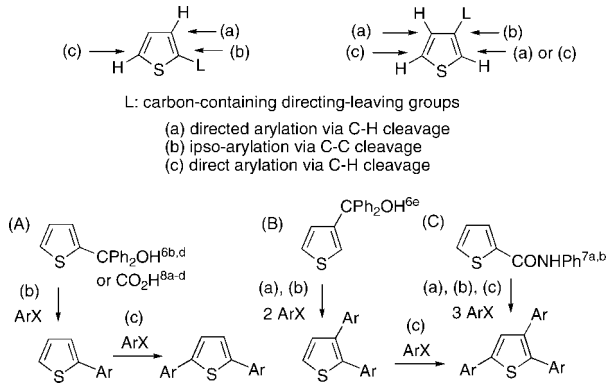
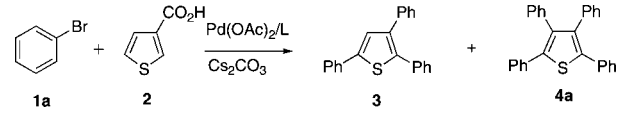
of a functional group in a given substrate to the metal center of a catalyst. As one of the representative reactions, we reported the palladium-catalyzed coupling of *tert*-benzyl alcohols with aryl halides.[6] Thus, the alcohols undergo not only ortho-arylation via C−H cleavage but also ipso-arylation via C−C cleavage. The precedence of the bond cleavages depends on both the substrate and catalyst structures.

Scheme 1. Pd-Catalyzed Arylation of 2- or 3-Functionalized Thiophenes with Aryl Halides



We also developed some selective multiple arylations of thiophene derivatives by utilizing the above strategy. In the palladium-catalyzed reaction of α,α-diphenyl-2-thiophenemethanol as an benzyl alcohol, the thienyl moiety was found to couple with aryl bromides or chlorides selectively via C−C cleavage with liberation of benzophenone to give 2-arylthiophenes (Scheme 1A), which can be further arylated directly at the 5 position via C−H cleavage.[6b,d] In contrast, α,α-diphenyl-3-thiophenemethanol undergoes sequential diarylation via initial C−H cleavage followed by C−C cleavage to give 2,3-diarylthiophenes selectively (Scheme 1B).[6e] In the related reaction of *N*-phenyl-2-thiophenecarboxamide with aryl bromides, 2,3,5-triarylthiophenes can be formed accompanied by cleavage of two C−H bonds and a formal decarbamoylation (Scheme 1C).[7a,b] On the other hand, it has recently been demonstrated that an unmodified smart carboxyl group on an aromatic ring can also act as both leaving and directing functions, and thus, benzoic acids undergo either ipso- or ortho-arylation.[8,9] In light of these results, while challenging, it is envisioned that perarylation would take place on *N*-phenyl-3-thiophenecarboxamide or 3-thiophenecarboxylic acid as substrate to give structurally and physically interesting tetraarylthiophenes if the three different arylation patterns could be suitably sequentialized under a certain single condition. In the course of our study of catalytic arylation reactions, we have succeeded in performing the multiple arylation efficiently by using 3-thiophenecarboxylic acid as well as its furan analogue as substrate, which is reported herein.[10,11]

Table 1. Reaction of 3-Thiophenecarboxylic Acid (**2**) with Bromobenzene (**1a**)[a]



entry	L	solvent	time (h)	% yield[b] 3	4a
1	PPh_3[c]	*o*-xylene	12	16	31
2	PCy_3	*o*-xylene	12	13[d]	51
3	PCy_2Ph	*o*-xylene	12	9[d]	47
4	P(biphenyl-2-yl)Cy_2	*o*-xylene	12	12	7
5	P(biphenyl-2-yl)$^tBu_2$	*o*-xylene	12	9	
6	PCy_3	mesitylene	8	14[d]	56
7[e]	PCy_3	mesitylene	8	14[d]	71
8[e]	PCy_3[c]	mesitylene	8	16	83 (82)[f]

[a] Reaction conditions: [**1a**]/[**2**]/[$Pd(OAc)_2$]/[L]/[Cs_2CO_3] = 2.5:0.5:0.05:0.1:2.5 (in mmol), in refluxing *o*-xylene (2.5 mL, bath temperature 160 °C) or mesitylene (5 mL, bath temperature 170 °C) under N_2. [b] GLC yield based on the amount of **2** used. [c] [L] = 0.2 mmol. [d] Formation of a small amount of an isomer was detected. [e] MS4Å (150 mg) was added. [f] Yield after isolation.

When 3-thiophenecarboxylic acid (**2**) (0.5 mmol) was treated with bromobenzene (**1a**) (2.5 mmol) in the presence of $Pd(OAc)_2$ (0.05 mmol) and PPh_3 (0.2 mmol) using Cs_2CO_3 (2.5 mmol) as base in refluxing *o*-xylene for 12 h, 2,3,4,5-tetraphenylthiophene (**4a**) (31%) was formed together with 2,3,5-triphenylthiophene (**3**) (16%) (entry 1 in Table 1). The reaction using PCy_3 (Cy = cyclohexyl) (0.1 mmol) as ligand in place of PPh_3 enhanced the yield of **4a** up to 51% (entry 2). While PCy_2Ph gave a similar result, P(biphenyl-2-yl)Cy_2 and P(biphenyl-2-yl)$^tBu_2$ were not effective (entries 3−5).

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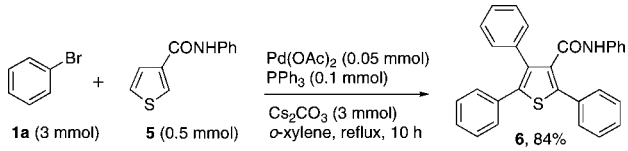
At an elevated temperature using mesitylene as solvent in the presence of PCy_3 (0.2 mmol) and with addition of molecular sieves 4Å (MS4Å) as desiccant, the tetraphenylated product **4a** was obtained in 83% yield (82% after isolation) (entry 8 versus entries 2, 6, and 7). It is noted that in some cases, formation of a small amount of an isomer of triphenylthiophene (presumably 2,3,4-isomer) was detected by GC−MS.

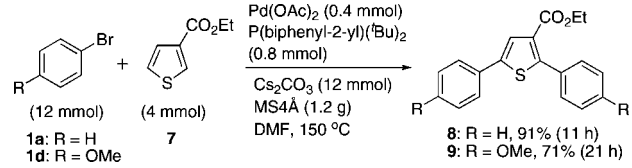
Scheme 2



It is worth noting that the reaction of *N*-phenyl-3-thiophenecarboxamide (**5**) with **1a** in *o*-xylene gave the corresponding 2,4,5-triphenylated product **6** in 84% yield (Scheme 2), suggesting that the amide function at the 3-position acts as a stable directing group as in *N*-phenylbenzamide.[7c]

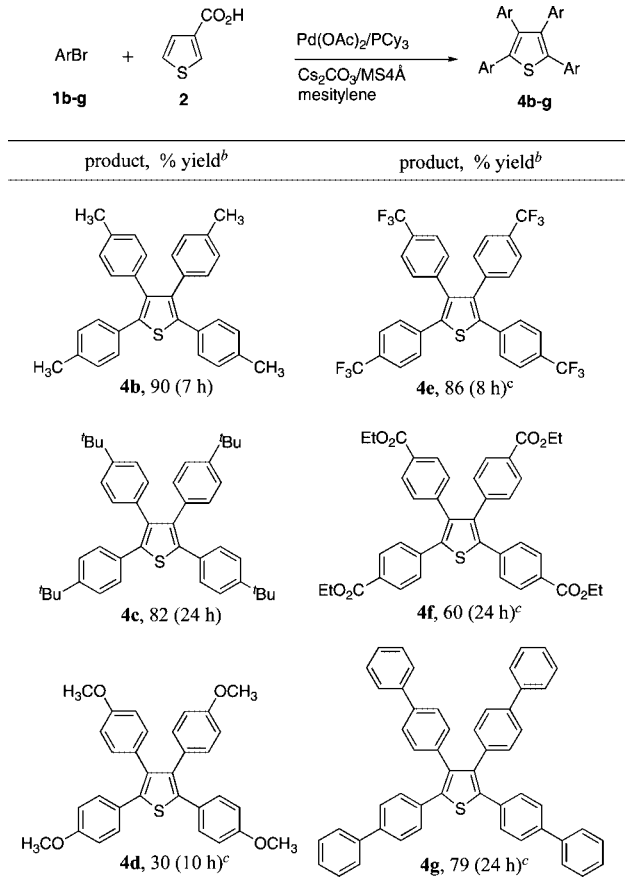
Table 2 summarizes the results for the reactions of 3-thiophenecarboxylic acid (**2**) with various 4-substituted aryl bromides **1b**−**g**. The reactions using electron-neutral and electron-deficient bromides, **1b**,**c** and **1e**,**f**, respectively, afforded the corresponding tetraarylthiophenes **4b**,**c**,**e**,**f** with good yields. Use of 4-bromoanisole (**1d**) also gave the expected compound **4d**, although the yield was low. 4-Bromobiphenyl (**1g**) was effectively applicable to afford **4g**.

Scheme 3



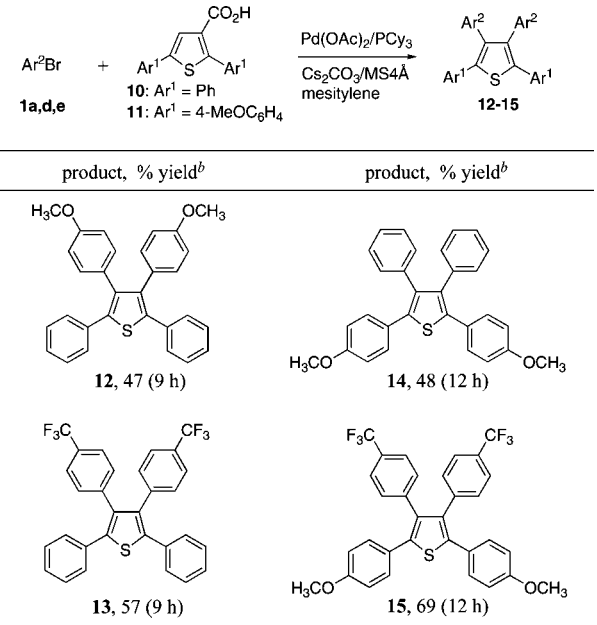
We next examined the preparation of tetraarylthiophenes having two different aryl groups at the 2,5- and 3,4-positions. The selective direct 2,5-diarylation of thiophenes having a nondirecting electron-withdrawing group at the 3-position is possible.[3] Thus, we prepared ethyl 2,5-diphenyl- (**8**) and 2,5-bis(4-methoxyphenyl)-3-thiophenecarboxylates (**9**) by the reaction of ethyl 3-thiophenecarboxylate (**7**) with bromides

Table 2. Reaction of 3-Thiophenecarboxylic Acid (**2**) with Various Aryl Bromides (**1b-g**)[a]



[a] Reaction conditions: [**1**]/[**2**]/[$Pd(OAc)_2$]/[PCy_3]/[Cs_2CO_3] = 2.5:0.5:0.05:0.2:2.5 (in mmol), MS4Å (150 mg), in mesitylene (5 mL) at 170 °C (bath temperature) under N_2 for 7−24 h. [b] Isolated yield. [c] [**1**] = 4.0 (in mmol).

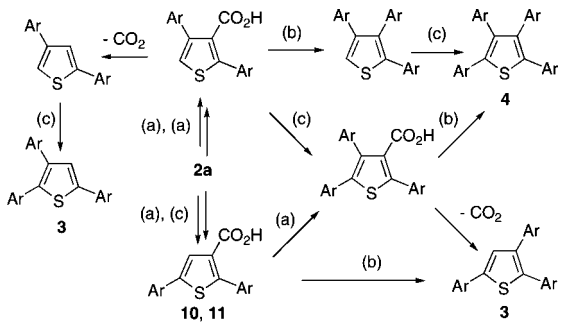
Table 3. Reaction of 2,5-Diaryl-3-thiophenecarboxylic Acids **10** and **11** with Aryl Bromides **1a**,**d**,**e**[a]



[a] Reaction conditions: [**1**]/[**10** or **11**]/[$Pd(OAc)_2$]/[PCy_3]/[Cs_2CO_3] = 1.5:0.5:0.05:0.2:1.5 (in mmol), MS4Å (150 mg), in mesitylene (5 mL) at 170 °C (bath temperature) under N_2. [b] Isolated yield.

1a and **1d** (Scheme 3).[6d] Then, free carboxylic acids **10** and **11** were treated with bromides **1a**, **1d**, or **1e**, and the expected tetraarylthiophenes **12**−**15** were obtained with moderate to good isolated yields (Table 3). In each case, formation of a minor amount of a separable triarylthiophene was detected by GC−MS.

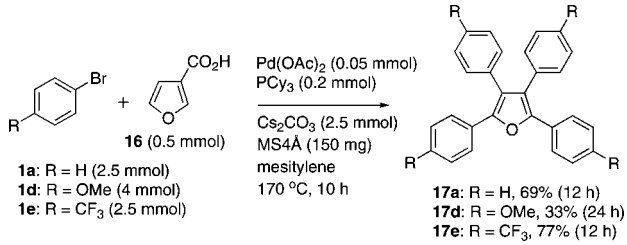
Scheme 4



As depicted in Scheme 1, the present reaction of **2** (L = 3-CO_2H) with **1** affording **4** may involve directed arylation (a), ipso-arylation (b), and direct arylation (c) (Scheme 4). The occurrence of decarboxylative arylation (b) at the 3-position after directed reaction (a) at the 4-position appears to lead to **4**. The reaction at 2- and 5-positions may take place in any sequences. The decarboxylative arylation (b) of 2,5-diarylthiphene-3-carboxylic acid (Table 3) or simple decarboxylation of 2,4-diaryl- and 2,4,5-triarylthiphene-3-carboxylic acids, provided this occurs, may lead to 2,3,5-triarylthiophene as unreactive byproduct. The major sequences leading to tri- and tetraarylthiophenes are, however, not definitive at the present stage. The success of the tetraarylaion appears to be due to the fact that the carboxyl function not only acts as a relatively stable anchor, but also it can be substituted at the suitable steps in the sequence.

We also examined the reaction of 3-furancarboxylic acid (**16**) with representative aryl bromides **1a**,**d**,**e**. As depicted in Scheme 5, the furan scaffold underwent tetraarylation, as 3-thiophenecarboxylic acid (**2**) did. The effect of substituents on the bromides seems to be comparable.

Scheme 5



In summary, we have demonstrated that 3-thiophenecarboxylic acid as well as its furan analogue undergoes a unique perarylation accompanied by cleavage of the three C−H bonds and decarboxylation upon treatment with aryl bromides in the presence of a palladium catalyst system. The 3,4-diarylation of 2,5-diaryl-3-thiophenecarboxylic acid has also been shown. The present method appears to provide a useful, straightforward synthetic route leading to tetraarylthiophenes and tetraarylfurans. Utilization of this strategy in other heterocyclic systems for making various π-conjugated compounds may be expected and will be examined in due course.

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Supporting Information Available: Standard experimental procedure and characterization data for new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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