JOC*Note*

Palladium-Catalyzed Selective 2,3-Diarylation of α,α-Disubstituted 3-Thiophenemethanols via Cleavage of C−H and C−C Bonds

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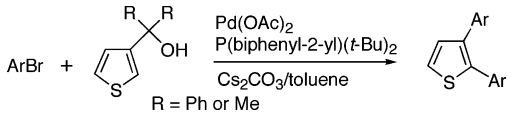

α,α-Disubstituted 3-thiophenemethanols undergo selective diarylation accompanied by cleavage of the C−H and C−C bonds of the 2- and 3-positions, respectively, upon treatment with aryl bromides in the presence of a palladium catalyst to give the corresponding 2,3-diarylthiophenes in good yields.

Poly- and oligoaryl compounds involving a thiophene unit have recently attracted much attention as the organic components of electronic devices.[1] Arylated thiophenes may also exhibit interesting biological activities.[2] One of the most useful methods to prepare such aryl heteroarenes is the palladium-catalyzed cross-coupling of aryl halides with heteroarylmetals or of heteroaryl halides with arylmetals.[3] It is also known that a number of five-membered heteroarenes including thiophenes can couple with aryl halides directly at their 2- and 5-positions under the influence of palladium catalysts.[4]

Meanwhile, catalytic reactions via cleavage of C−H[4,5] and C−C[6] 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 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.[7] The reaction proceeds not only via C−H cleavage but also via C−C cleavage in the key arylpalladium(II) alcoholate species (Scheme 1). The precedence of the bond cleavages depends on both the substrate and catalyst structures. In the reaction using α,α-diphenyl-2-thiophenemethanol as a heterocyclic substrate, the thienyl moiety was found to couple with aryl halides selectively via C−C cleavage with extrusion of benzophenone to give 2-arylthiophenes, which can be further arylated at the 5 position via C−H cleavage (Scheme 2, a).[7b,d] In our continuous study of catalytic arylation, we observed that in sharp contrast to the reaction of the 2-thiophenemethanol derivative, its 3-thienyl isomer undergo sequential diarylation via initial C−H cleavage followed by C−C cleavage to give 2,3-diarylthiophenes selectively (Scheme 2, b), which is reported herein.

When α,α-diphenyl-3-thiophenemethanol (**2a**) (0.5 mmol) was treated with bromobenzene (**1a**) (2 mmol) in the presence of $Pd(OAc)_2$ (0.05 mmol) and PPh_3 (0.2 mmol) using Cs_2CO_3 (2 mmol) as base in refluxing toluene for 10 h, 2,3-diphenylthiophene (**3a**) (58%) was formed together with 2,3,5-triphenylthiophene (**4**) (41%) (Table 1, entry 1). The reaction using PCy_3 or P(biphenyl-2-yl)(*t*-Bu)$_2$ (0.1 mmol) as ligand in place of PPh_3 also gave **3a** and **4** (entries 2 and 3). Notably, with the latter ligand, the diphenylated product **3a** was produced selectively in 86% yield. At an elevated temperature in refluxing *o*-xylene in the presence of PPh_3 or PCy_3 (entries 4 and 5), the triphenylated product **4** was obtained as the predominant product, whereas using the bulky biphenylphosphine a considerable amount of **3a** remained (entry 6). These results indicate that all the ligands examined can promote the phenylation at the 2- and 5-positions via C−H cleavage and that at the 3-position via C−C cleavage, while the reaction of the 5-position is relatively slow, especially with the biphenylphosphine ligand.

Monitoring the reaction of **2a** with **1a** under the conditions for entry 3 by GC−MS confirmed that in the early stage, a considerable amount of monophenylated product, that is α,α,2-triphenyl-3-thiophenemethanol, is found together with **3a** and the former is disappeared to afford **3a** as the predominant

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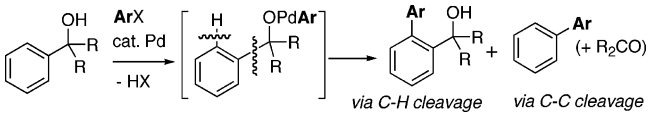
SCHEME 1



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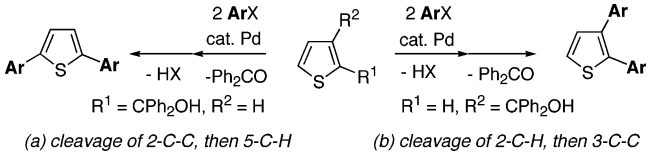

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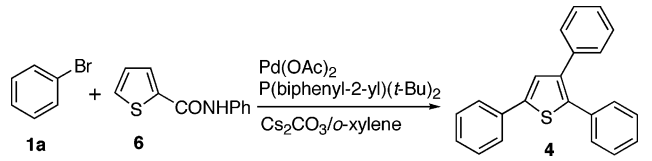

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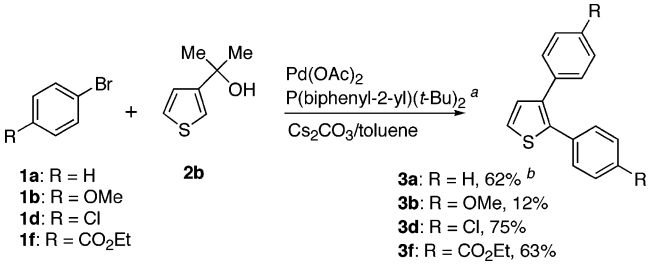
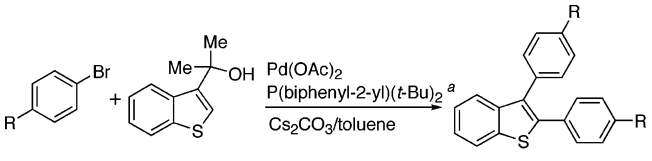


[a] Reaction conditions: [**1**]/[**2**]/[Pd(OAc)$_2$]/[ligand]/[Cs_2CO_3] = 2:0.5:0.05:0.1:2 (in mmol), in refluxing toluene under N_2 for 8 h. [b] Determined by GC.

SCHEME 5

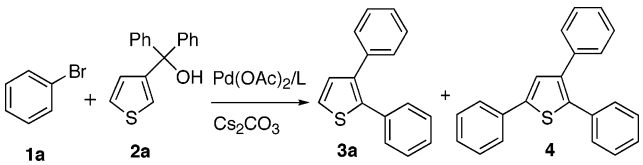


[a] Reaction conditions: [**1**]/[**2**]/[Pd(OAc)$_2$]/[ligand]/[Cs_2CO_3] = 2:0.5:0.05:0.1:2 (in mmol), in refluxing toluene under N_2 for 8 h. [b] Determined by GC. The value in parentheses is the isolated yield.

product along with **4**. This observation is consistent with the successive 2,3-diphenylation in this order.

We previously reported that *N*-phenyl-2-thiophenecarboxamide also undergoes triphenylation upon treatment with excess bromobenzene under similar conditions to give **4** (Scheme 3).[8] The reaction is considered to proceed through coordination-assisted 3-phenylation followed by either 5-phenylation or decarbamoylation at the 2-position, and thus, both 2,4- and 2,3-diphenylthiophenes are formed in comparable amounts as the precursors of **4**. In contrast, in the reaction of **2a**, participation

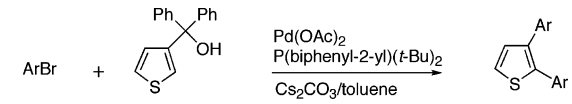
TABLE 1. Reaction of α,α-Diphenyl-3-thiophenemethanol (2a) with Bromobenzene (1a)[a]

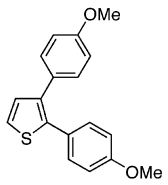
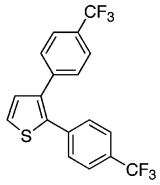
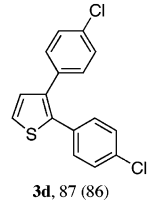
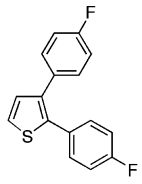
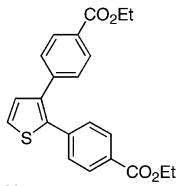
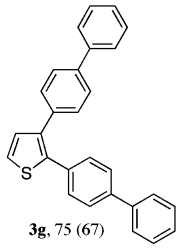


			% yield [b]	
entry	L	solvent	**3a**	**4**
1	PPh_3[c]	toluene	58	41
2	PCy_3	toluene	72	20
3	P(biphenyl-2-yl)(*t*-Bu)$_2$	toluene	86	10
4	PPh_3[c]	*o*-xylene	4	91
5	PCy_3	*o*-xylene	5	92
6	P(biphenyl-2-yl)(*t*-Bu)$_2$	*o*-xylene	39	57

[a] Reaction conditions: [**1a**]/[**2a**]/[Pd(OAc)$_2$]/[L]/[Cs_2CO_3] = 2:0.5:0.05:0.1:2 (in mmol), in refluxing toluene or *o*-xylene under N_2 for 10 h. [b] GLC yield based on the amount of **2a** used. [c] [L] = 0.2 mmol.

TABLE 2. Reaction of α,α-Diphenyl-3-thiophenemethanol (2a) with Various Aryl Bromides (1b−g)[a]



product, % yield [b]	
	
3b, 86 (60)	**3c**, (64)
	
3d, 87 (86)	**3e**, 91 (66)
	
3f, 94 (83)	**3g**, 75 (67)

[a] Reaction conditions: [**1a**]/[**2a**]/[Pd(OAc)$_2$]/[ligand]/[Cs_2CO_3] = 2:0.5:0.05:0.1:2 (in mmol), in refluxing toluene under N_2 for 8−10 h. [b] Determined by GC. The value in parentheses is the isolated yield.

of the 2,4-isomer is, if any, negligible and the 2,3-isomer **3a** can be obtained effectively under controlled conditions, which appeared to be a remarkable aspect. Consequently, we next undertook the preparation of various 2,3-diarylthiophenes by the present method.

Table 2 summarizes the results for the reactions of the thiophenemethanol **2a** with various aryl bromides **1b**−**g**. The diarylation proceeded effectively using both electron-rich bromide **1b** and those having an electron-withdrawing substituent **1c**−**f** to give **3b**−**f**. 4-Bromobiphenyl (**1g**) was also applicable to afford **3g**.

2-(Thienyl-3-yl)-2-propanol (**2b**) and its benzothiophene analogue **2c** in place of **2a** could also be reacted with a number of aryl bromides to afford the corresponding 2,3-diarylated

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products **3** and **5** with substantial yields with the exception of the coupling of **2b** with **1b** (Schemes 4 and 5). In the latter case, a considerable amount of the starting alcohol was recovered. The reason the combination is sluggish is not definitive at the present stage.

In summary, we have shown that α,α-disubstituted 3-thiophenemethanols undergo selective 2,3-diarylation accompanied by cleavage of the C−H and C−C bonds of 2- and 3-positions, respectively, by treatment with aryl bromides in the presence of a palladium catalyst system. This appears to provide a useful, general synthetic route leading to 2,3-diarylthiophenes.

Experimental Section

2,3-Bis(4-methoxyphenyl)thiophene (3b). In a 20 mL two-necked flask were added the bromide **1b** (2 mmol, 374 mg), the alcohol **2a** (0.5 mmol, 133 mg), $Pd(OAc)_2$ (0.05 mmol, 11.2 mg), P(biphenyl-2-yl)(*t*-Bu)$_2$ (0.1 mmol, 20.1 mg), Cs_2CO_3 (2 mmol, 652 mg), 1-methylnaphthalene (ca. 50 mg) as internal standard, and toluene (2.5 mL). The resulting mixture was stirred under N_2 (balloon) at 130 °C (bath temperature) for 8 h. After cooling, analysis of the mixture by GC confirmed formation of compound **3b** (127 mg, 86%). The product (89 mg, 60%) was also isolated by filtration of the mixture with a filter paper with ether, evaporation of the solvents, and chromatography on silica gel using hexanes−ethyl acetate (98:2, v/v). Compound **3b**:[2b] mp 105−106 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.80 (s, 3H), 6.79−6.84 (m, 4H), 7.10 (d, J = 5.1 Hz, 1H), 7.19−7.25 (m, 4H), 7.25 (d, J = 5.4 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 55.2, 55.2, 113.8, 113.9, 123.30 127.0, 129.2, 130.1, 130.3, 130.5, 137.0, 137.7, 158.4, 158.9; MS *m*/*z* 296 (M^+). Anal. Calcd for $C_{18}H_{16}O_2S$: C, 72.94; H, 5.44. Found: C, 72.76; H, 5.26.

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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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