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Palladium-catalyzed Direct Monoarylation of Thiophene-, Benzothiophene-, and Indoleacetic Acids through Regioselective C–H Bond Cleavage

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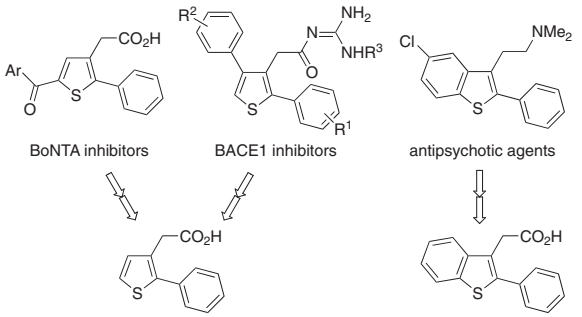
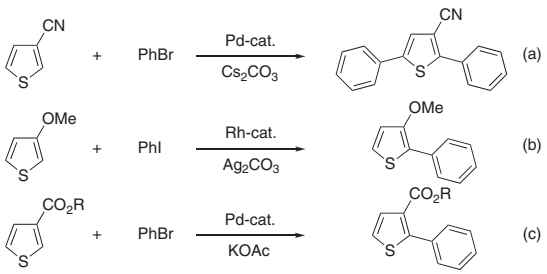
Regioselective monoarylation of thiophene-3-acetic acid with aryl bromides proceeds efficiently under palladium catalysis to selectively give the corresponding C2-arylated thiophene derivatives. The procedure is also applicable to the C2-arylations of benzothiophene-3- and indole-3-acetic acids.

Since 2-arylthiophene frameworks can be seen in a wide range of biologically active agents,[1] the development of methods for their effective construction has attracted considerable attention. 2-Arylthiophene-3- and 2-arylbenzothiophene-3-acetic acids are known as their key synthetic intermediates (Scheme 1).[1]

Among promising methods for making a thienyl–aryl bond is transition-metal-catalyzed direct arylation on thiophenes with aryl halides.[2] For example, we have reported that 3-cyanothiophene undergoes palladium-catalyzed arylation efficiently at the C2- and C5-positions (Scheme 2a).[3] As in this example, it is known that diarylated together with monoarylated products are usually formed, often predominantly, in the reaction of 2,5-unsubstituted thiophenes. Thus, the regioselective monoarylation has so far been limited to only a few examples including those of 3-methoxy-[4] and 3-alkoxycarbonylthiophenes[5] (Schemes 2b and 2c).



Scheme 1.

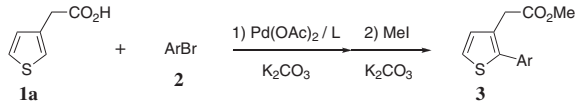


Scheme 2.

In the context of our study of the direct functionalization of heteroarenes,[6] we have undertaken the palladium-catalyzed arylation of thiophene-3- and benzothiophene-3-acetic acids with aryl bromides. As a result, the reaction has been found to take place selectively at the C2-position to produce 2-arylthiophene-3- and 2-arylbenzothiophene-3-acetic acid derivatives. The new findings are described herein.

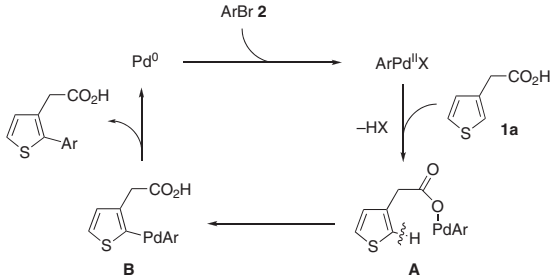
In an initial attempt, thiophene-3-acetic acid (**1a**) (0.4 mmol) was treated with bromobenzene (**2a**) (0.5 mmol) in the presence of $Pd(OAc)_2$ (0.02 mmol), biphenyl-2-yldicyclohexylphosphane (L1, 0.04 mmol), and K_2CO_3 (0.6 mmol) as catalyst, ligand, and

Table 1. Reaction of thiophene-3-acetic acid (**1a**) with aryl bromides **2**[a]

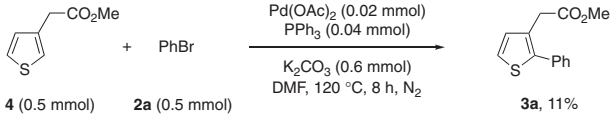


Entry	2	L (mmol)[b]	Temp/°C	Product(s), Yield/%[c]
1[d]	**2a**: R = H	L1 (0.04)	120	**3a**: R = H, 81[e]
2	**2a**: R = H	L1 (0.04)	120	**3a**: R = H, 85
3	**2a**: R = H	L2 (0.04)	120	**3a**: R = H, 94 (90)
4	**2b**: R = Me	L1 (0.04)	120	**3b**: R = Me, >99 (85)
5	**2c**: R = OMe	L1 (0.08)	120	**3c**: R = OMe, 78 (64)
6	**2d**: R = Cl	L1 (0.04)	100	**3d**: R =Cl, 89 (80)
7	**2e**: R = CF_3	L2 (0.04)	85	**3e**: R = CF_3, 93 (84)
8	**2f**: R = CO_2Et	L2 (0.04)	85	**3f**: R = CO_2Et, 95 (92)
9	**2g**: R = CN	L2 (0.04)	85	**3g**: R = CN, >99 (92)
10	**2h**	L1 (0.04)	120	**3h**, 99 (82)
11	**2i**	L1 (0.08)	120	**3i**, 65 (65)

[a]Reaction conditions: 1) **1a** (0.5 mmol), **2** (0.4 mmol), $Pd(OAc)_2$ (0.02 mmol), K_2CO_3 (0.6 mmol), in DMF (2.5 mL) for 8 h under N_2; 2) with the addition of MeI (6 mmol) and K_2CO_3 (3 mmol) at room temperature for 3 h. [b]L1 = biphenyl-2-yldicyclohexylphosphane, L2 = PPh_3. [c]GC yield based on the amount of **2** used. Value in parentheses indicates yield after isolation. [d]**1a** (0.4 mmol) and **2a** (0.5 mmol) were used. [e]Minor amounts of diphenylated products were also formed (total 17%).

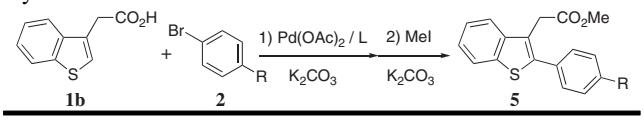


Scheme 3.



Scheme 4.

Table 2. Reaction of benzo[*b*]thiophene-3-acetic acid (**1b**) with aryl bromides **2**[a]

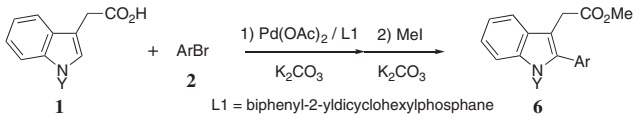


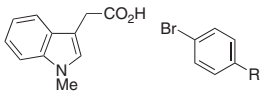
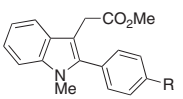
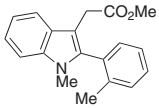
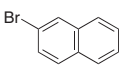
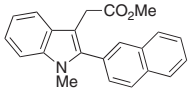
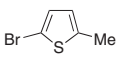
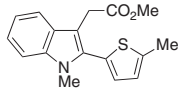
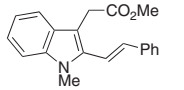
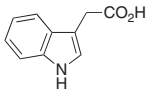
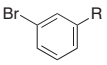
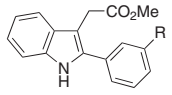
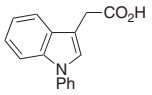
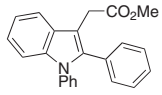
Entry	2	R	L (mmol)[b]	Temp /°C	Product, Yield/%[c]
1	**2a**	R = H	L2 (0.04)	120	**5a**: R = H, 94
2	**2a**	R = H	L2 (0.04)	100	**5a**: R = H, >99 (99)
3	**2a**	R = H	L1 (0.04)	100	**5a**: R = H, 90
4	**2b**	R = Me	L1 (0.08)	100	**5b**: R = Me, >99 (96)
5	**2c**	R = OMe	L1 (0.08)	100	**5c**: R = OMe, 80 (68)
6	**2d**	R = Cl	L1 (0.04)	100	**5d**: R = Cl, 81 (61)
7	**2e**	R = CF_3	L2 (0.04)	100	**5e**: R = CF_3, 91 (74)
8	**2e**	R = CF_3	L2 (0.04)	85	**5e**: R = CF_3, 78

[a]Reaction conditions: 1) **1b** (0.4 mmol), **2** (0.5 mmol), $Pd(OAc)_2$ (0.02 mmol), K_2CO_3 (0.6 mmol), in DMF (2.5 mL) for 8 h under N_2; 2) with the addition of MeI (6 mmol) and K_2CO_3 (3 mmol) at room temperature for 3 h. [b]L1 = biphenyl-2-yldicyclohexylphosphane, L2 = PPh_3. [c]GC yield based on the amount of **1b** used. Value in parentheses indicates yield after isolation.

base, respectively, in DMF at 120 °C for 8 h under N_2. After the subsequent methyl esterification using iodomethane for quantification, the C2-monophenylated product **3a** was obtained in 81% yield, along with minor amounts of diphenylated products (total 17%) (Entry 1 in Table 1). In the presence of a slight excess of **1a**, formation of diphenylated products was completely suppressed to selectively give **3a** in 85% yield (Entry 2). Less expensive PPh_3 (L2) could also be employed as ligand (Entry 3). Using L1 at 120 or 100 °C, the reactions of **1a** with methyl- (**2b**), methoxy- (**2c**), and chloro- (**2d**) substituted bromobenzenes proceeded smoothly to produce the corresponding C2-arylated products **3b**–**3d** (Entries 4–6). In these cases, the use of L2 as ligand decreased the product yields due to contamination by phenyl groups from L2 to form small amounts of **3a**.[7] In contrast, in the reactions of electron-deficient bromobenzenes **2e**–**2g** reacting with **1a**, such contamination was

Table 3. Reaction of indole-3-acetic acids **1** with aryl bromides **2**[a]



Entry	1	2	Temp/°C	Product, Yield/%[b]
				
1	**1c**	**2a**: R = H	120	**6a**: R = H, >99 (93)
2		**2b**: R = Me	120	**6b**: R = Me, (94)
3		**2c**: R = OMe	120	**6c**: R = OMe, (94)
4		**2d**: R = Cl	120	**6d**: R = Cl, (91)
5		**2e**: R = CF_3	120	**6e**: R = CF_3, (91)
6		**2f**: R = CO_2Et	120	**6f**: R = CO_2Et, (86)
7		**2g**: R = CN	120	**6g**: R = CN, (87)
8		**2j**: R = CHO	120	**6h**: R = CHO, (79)
9		**2k**: R = 4-R′C_6H_4 (R′ = pentyl)	120	**6i**: R = 4-R′C_6H_4, (84) (R′ = pentyl)
				
10[c]	**1c**	**2l**	140	**6j**, (79)
				
11	**1c**	**2h**	120	**6k**, (87)
				
12[c]	**1c**	**2i**	140	**6l**, (60)
				
13[d]	**1c**	**2m**	120	**6m**, (41)
				
14	**1d**	**2a**: R = H	140	**6n**: R = H, (75)
15		**2n**: R = Me	140	**6o**: R = Me, (78)
16		**2o**: R = Cl	140	**6p**: R = Cl, (74)
				
17	**1e**	**2a**	120	**6q**, (84)

[a]Reaction conditions: 1) **1** (0.4 mmol), **2** (0.5 mmol), $Pd(OAc)_2$ (0.008 mmol), biphenyl-2-yldicyclohexylphosphane (0.016 mmol), K_2CO_3 (0.9 mmol), in DMF (2.5 mL) for 8 h under N_2; 2) with the addition of MeI (5 mmol) and K_2CO_3 (1 mmol) at room temperature for 3 h. [b]GC yield based on the amount of **1** used. Value in parentheses indicates yield after isolation. [c]biphenyl-2-yldicyclohexylphosphane (0.032 mmol) was used. [d]Without biphenyl-2-yldicyclohexylphosphane.

not observed even using L2 at 85 °C to afford **3e–3g** in good yields (Entries 7–9). Besides bromobenzenes, 2-bromonaphthalene (**2h**) and 2-bromo-5-methylthiophene (**2i**) also underwent the reaction with **1a** in the presence of L1 (Entries 10 and 11).

A plausible mechanism for the arylation of **1a** with **2** is illustrated in Scheme 3, in which neutral ligands are omitted. First, oxidative addition of **2** toward Pd^0 species generated in situ followed by ligand exchange with **1a** gives an arylpalladium carboxylate intermediate **A**. Then, directed palladation[8] on the thiophene ring may occur to form an aryl(thienyl)palladium species **B**. Final reductive elimination affords a C2-arylated product and regenerates Pd^0 species. It should be noted that treatment of methyl thiophene-3-acetate with **2a** gave **3a** only in a low yield (Scheme 4). Therefore, coordination of the carboxylic group of **1a** appears to be the key for the effective palladation in **A**.[9]

Benzo[*b*]thiophene-3-acetic acid (**1b**) also underwent the phenylation upon treatment with **2a** in the presence of the $Pd(OAc)_2$/L2 catalyst system at 120 °C to afford the corresponding C2-phenylated product **5a** in 94% yield (Entry 1 in Table 2). At 100 °C, **5a** was obtained quantitatively (Entry 2). In the reactions of **2b–2d** with **1b**, L1 was used in place of L2 to avoid the contamination as in the reaction with **1a** (Entries 4–6). In the cases using **2b** and **2c**, addition of the increased amount of L1 improved the product yields. The reaction of **1b** with **2e** took place efficiently in the presence of the $Pd(OAc)_2$/L2 catalyst system at 100 °C, rather than at 85 °C (Entry 7 vs. 8).

Nitrogen-containing analogs, 2-arylindole-3-acetic acids, have also attracted attention because of their interesting biological properties.[10] Therefore, we next examined their synthesis through the direct arylation of readily available indole-3-acetic acids. Treatment of *N*-methylindole-3-acetic acid (**1c**) (0.4 mmol) with **2a** (0.5 mmol) in the presence of $Pd(OAc)_2$ (0.008 mmol), L1 (0.016 mmol), and K_2CO_3 (0.9 mmol) in DMF at 120 °C for 8 h under N_2 and subsequent methyl esterification gave a C2-phenylated product **6a** in a quantitative yield (Entry 1 in Table 3). Under the same conditions, a number of 4-substituted bromobenzenes **2b–2k** reacted with **1c** efficiently to produce the corresponding 2-arylindole derivatives (Entries 2–9). Similarly, 2-bromotoluene (**2l**), 2-bromonaphthalene (**2h**), 2-bromo-5-methylthiophene (**2i**), and β-bromostyrene (**2m**, E:Z = 6.5:1) underwent the reaction at 120–140 °C (Entries 10–13). In the case with **2m**, the product yield was decreased by the addition of L1 or L2. The arylation of *N*-unsubstituted and *N*-phenylated indole-3-acetic acids, **1d** and **1e**, with bromides **2a**, **2n**, and **2o** took place effectively to form products **6n–6q** in 74–84% yields (Entries 14–17).

In summary, we have demonstrated that thiophene-3-, benzothiophene-3-, and indole-3-acetic acids undergo regioselective arylation upon treatment with aryl bromides under palladium catalysis to afford the corresponding C2-arylated products of pharmaceutical interest.[11]

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