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Palladium-catalyzed direct arylation of thiazoles with aryl bromides

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Abstract—Thiazole, 2-phenyl or -alkyl substituted one and benzothiazole are efficiently arylated with aryl bromides at the 2- and/or 5-position(s) in the presence of $Pd(OAc)_2$ and a bulky phosphine ligand using Cs_2CO_3 as base. 2-Phenyl-5-thiazolecarboxanilide undergoes successive diarylation at the 4- and 5-positions accompanied by decarbamoylation.

1. Introduction

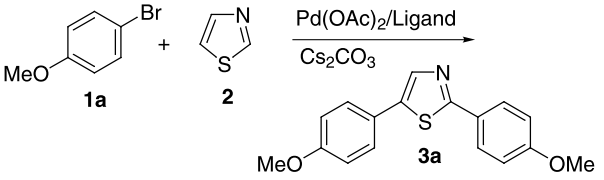
Various thiazole derivatives are known to exhibit pharmacological activities.[1] Aryl-substituted thiazoles are of importance not only as medicinal agents,[1] but also as organic functional materials such as fluorescent dyes[2a,b] and liquid crystals.[2b,c] Among the most useful methods to prepare such arylheterocycles is the palladium-catalyzed cross-coupling of either heteroaryl halides with arylmetals or aryl halides with heteroarylmetals.[3] Thus, the reaction has been extensively studied.

Meanwhile, it is known that aryl halides can couple directly with a number of five-membered heteroaromatics including thiazoles at their 2- and/or 5-position(s) in the presence of a palladium catalyst.[4] This method has a significant advantage, not requiring stoichiometric metalation of the heterocycles. We previously reported that azole compounds and thiophenes were effectively arylated using aryl bromides or iodides in the presence of $Pd(OAc)_2$–PPh_3 and K_2CO_3 or Cs_2CO_3, as catalyst and base, respectively.[5a] For sulfur-containing substrates, i.e. thiazoles and thiophenes, addition of a copper(I) halide such as CuI as a promoter or a cocatalyst was required to perform the reaction effectively. After that, it was also found that by using bulky phosphine ligands, which may yield coordinatively unsaturated active palladium species,[6] the arylation of 2- or 3-substituted thiophenes with aryl bromides proceeded efficiently without adding the copper species.[5b] Therefore, it was anticipated that thiazoles could also be arylated effectively under similar conditions. Consequently, the arylation reaction of thiazoles has been investigated further. The results are described herein.

2. Results and discussion

The arylation of unsubstituted thiazole (**2**) was first carried out using various tertiary phosphines in order to examine the effect of ligands on the reaction. As the arylating reagent, 4-bromoanisole (**1a**) (Table 1) was employed, since an electron-donating substituent on aryl halides often causes a significant problem, that is scrambling of the aryl moieties with those of triarylphosphines.[7] When **2** (1 mmol) was treated with **1a** (2.4 mmol) in the presence of $Pd(OAc)_2$ (0.1 mmol) and PPh_3 (0.2 mmol) using Cs_2CO_3 as base in DMF at 150°C for 4 h, 2,5-di(4-anisyl)thiazole (**3a**) was

Table 1. Reaction of thiazole (**2**) with 4-bromoanisole (**1a**)



Entry	Ligand	Ligand/Pd	% Yield **3b**[a]
1[b]	PPh_3	2	6
2	$P(4\text{-}MeOC_6H_4)_3$	2	28
3	$P(t\text{-}Bu)_3$	2	76 (66)
4	$P(biphenyl\text{-}2\text{-}yl)(t\text{-}Bu)_2$	2	78
5	$P(2\text{-}MeC_6H_4)_3$	2	3
6	$P(cyclohexyl)_3$	2	8
7	$P(t\text{-}Bu)_3$	1	39
8	$P(t\text{-}Bu)_3$	3	42
9[c]	$P(t\text{-}Bu)_3$	2	53
10[d]	$P(t\text{-}Bu)_3$	2	16

Reaction conditions: [**1a**]/[**2**]/[$Pd(OAc)_2$]/[Cs_2CO_3]=2.4:1:0.1:2.4 (in mmol), in DMF at 150°C for 4 h under N_2.
[a] Determined by GC. The value in parentheses is isolated yield.
[b] Anisyl(phenyl)thiazoles (ca. 15%) were also formed.
[c] K_2CO_3 was used in place of Cs_2CO_3.
[d] *o*-Xylene was used in place of DMF.

Keywords: arylation; aryl halides; palladium and compounds; thiazoles.
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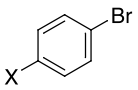
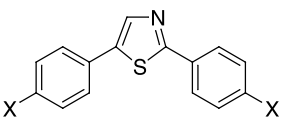
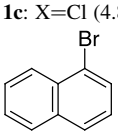
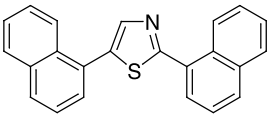
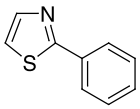
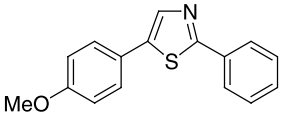
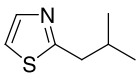
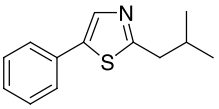
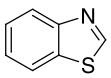
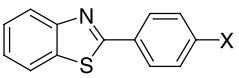
formed in only 6% yield together with trace amounts of anisyl- and phenylthiazoles and ca. 15% combined yield of two possible anisylphenylthiazoles, which was confirmed by GC and GC–MS (entry 1). The formation of the phenyl-containing products suggests that the undesired scrambling occurred. Using P(4-MeOC$_6$H$_4$)$_3$ to avoid the scrambling improved the product yield, but it was still low (entry 2). In expectation, a bulky phosphine P(*t*-Bu)$_3$ remarkably promoted the reaction to give **3a** in 76% (entry 3), no scrambling being observed. Almost the same product yield was obtained using double amounts of the substrates (Table 2, entry 1). Another bulky phosphine P(biphenyl-2-yl)(*t*-Bu)$_2$[8] showed similar performance (entry 4), whereas P(2-MeC$_6$H$_4$)$_3$ and P(cyclohexyl)$_3$ could not enhance the reaction (entries 5 and 6). The amount of ligand was also an important factor determining the reaction efficiency (entries 3, 7 and 8). A maximum yield was obtained at a P/Pd ratio of 2. Use of K_2CO_3 in place of Cs_2CO_3 as base retarded the reaction (entry 9). *o*-Xylene as solvent was not effective for this reaction (entry 10).[5b] It is noted that in each run, formation of the singly arylated products was not detected or negligible even at the early stage of the reaction, suggesting that the second arylation is significantly faster than the first one. Thus, the precedence of 2- and 5-arylations under the present conditions is not definitive.[9]

Table 2 summarizes the results for the arylation of **2**, 2-phenylthiazole (**4**), 2-isobutylthiazole (**5**) and benzothiazole (**6**) using Pd(OAc)$_2$ and P(*t*-Bu)$_3$ or P(biphenyl-2-yl)(*t*-Bu)$_2$ in the presence of Cs_2CO_3 in DMF. The reactions of **2** with bromobenzene (**1b**), 4-bromochlorobenzene (**1c**) and 1-bromonaphthalene (**1d**) gave the corresponding 2,5-diarylated thiazoles **3b–d** in good yields, as did that with **1a** (entries 1–5). The 5-arylations of **4** with **1a** and of **5** with **1b** proceeded smoothly (entries 6 and 8). The 2-arylation of **6** with **1a–c** also took place to give 2-arylbenzothiazoles

Table 2. Reaction of thiazoles **2** and **4–6** with aryl bromides **1**

Entry	Bromide (mmol)	Thiazole (mmol)	Ligand[a]	Time (h)	Product, % yield[b]
					
1	**1a**: X=OMe (4.8)	**2** (2)	L1	8	**3a**: X=OMe, 78 (69)
2	**1b**: X=H (4.8)	**2** (2)	L1	8	**3b**: X=H, 90 (70)
3	**1b**: X=H (4.8)	**2** (2)	L2	3	**3b**: X=H, 95 (76)
4	**1c**: X=Cl (4.8)	**2** (2)	L1	10	**3c**: X=Cl, 76 (63)
					
5	**1d** (4.8)	**2** (2) 	L1	8	**3d**, 78 (55) 
6	**1a** (1.2)	**4** (1)	L2	5	**7**, 88 (72)
7[c]	**1a** (1.2)	**4** (1) 	L2	18	**7**, 72 
8[d]	**1b** (1.2)	**5** (1) 	L1	1	**8**, 93 (71) 
9[e]	**1a** (1)	**6** (1.2)	L1	1	**9a**: X=OMe, 56
10[e]	**1a** (1)	**6** (1.2)	L1	4	**9a**: X=OMe, 75
11[e,f]	**1a** (1)	**6** (1.2)	L1	1	**9a**: X=OMe, 76 (71)
12[e]	**1b** (1)	**6** (1.2)	L1	1	**9b**: X=H, 65
13[e,f]	**1b** (1)	**6** (1.2)	L1	1	**9b**: X=H, 76 (63)
14[e,f]	**1c** (1)	**6** (1.2)	L1	1	**9c**: X=Cl, 75 (45)

The reaction was carried out using Pd(OAc)$_2$-ligand(0.05 and 0.1 equiv. to thiazole) and Cs_2CO_3 (equimolar amount to **1**) in DMF at 150°C under N_2 unless otherwise noted.

[a] L1=P(*t*-Bu)$_3$, L2=P(biphenyl-2-yl)(*t*-Bu)$_2$.

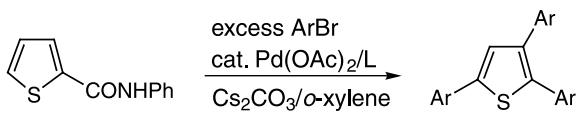
[b] Determined by GC. The value in parentheses is isolated yield.

[c] Reaction in *o*-xylene.

[d] Pd(OAc)$_2$-ligand (0.1 and 0.2 equiv to **5**).

[e] Pd(OAc)$_2$-ligand (0.05 and 0.1 equiv to **1**).

[f] CuBr (0.2 mmol) was added.



Scheme 1.

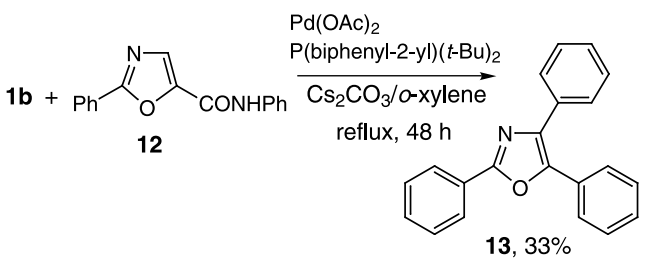
9a–c. It is noted that addition of a catalytic amount of CuBr to the reaction of **6** somewhat enhanced the reaction (entries 9 and 12 vs 11 and 13).

In the previous study of thiophene arylation, it was also found that 2-thiophenecarboxamides underwent an unprecedented multiple arylation on treatment with excess aryl bromides (Scheme 1).[5b] In this reaction, the carbamoyl group acts as a directing group for the arylation at the 3-position, after which it is cleaved and the 2-position as well as the 5-position is arylated to give 2,3,5-triarylthiophenes. The reaction seems to be useful as a unique method for the successive arylation of the β- and α-positions.

Consequently, the arylation of thiazole nucleus was examined in order to see applicability of the method. Due to its ready availability, 2-phenyl-5-thiazolecarboxanilide (**10**) was employed as substrate. The reaction of **10** with **1a** in the presence of $Pd(OAc)_2$, P(biphenyl-2-yl)(t-Bu)$_2$ and Cs_2CO_3 in o-xylene could occur accompanied by decarbamoylation to give the expected product, 4,5-di(4-anisyl)-2-phenylthiazole (**11a**) in 67% yield (Table 3, entry 1).[10] Similarly, treatment of **10** with **1b**, **1c** and 4-bromobiphenyl (**1e**) in o-xylene afforded the corresponding 4,5-diaryl-2-phenylthiazoles **11b**, **11c** and **11e**.

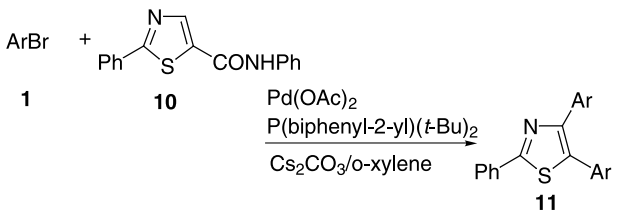
It should be noted that the reaction of **10** with **1a** did not proceed in DMF. This may be due to the fact that the first 4-arylation is difficult to occur in a polar solvent, in which directing effect of the amide function seems to be hampered.[11] This contrasts with the fact that the 5-arylation of **4** in DMF was faster than that in o-xylene (see Table 2, entries 6 and 7). This may be attributed to electrophilic character of the latter reaction.[5a,9b]

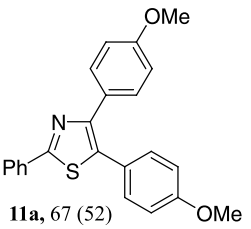
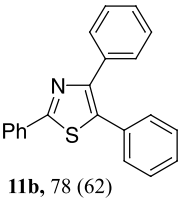
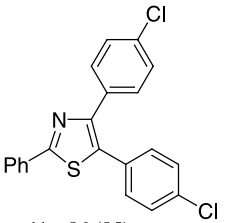
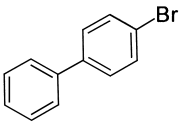
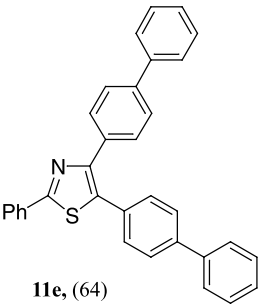
As an additional experiment, 2-phenyl-5-oxazolecarboxanilide (**12**) was treated with **1b** under the same conditions with those employed in entry 2 of Table 3, in order to compare the reactivity of it with that of **10**. While the expected product, 2,4,5-triphenyloxazole (**13**) (33%) was obtained (Scheme 2), a considerable amount of 2,4-



Scheme 2.

Table 3. Reaction of 2-phenyl-5-thiazolecarboxanilide (**10**) with aryl bromides (**1**)



Entry	ArBr	Time (h)	Product, % yield[a]
1	**1a**	24	 **11a,** 67 (52)
2	**1b**	48	 **11b,** 78 (62)
3	**1c**	24	 **11c,** 86 (85)
4	 **1e**	48	 **11e,** (64)

Reaction conditions: [**1**]/[**10**]/[$Pd(OAc)_2$]/[ligand]/[Cs_2CO_3]=2.5:0.5:0.05:0.1:2.5 (in mmol), in refluxing o-xylene under N_2.

[a] Determined by GC. The value in parentheses is isolated yield.

diphenyloxazole (ca. 20%) was accompanied. This result suggests that the latter oxazole is less reactive than the corresponding thiazole under the conditions employed.

In summary, we have described that the palladium-catalyzed direct arylation of thiazole at the 2- and 5-positions with aryl bromides proceeds efficiently using a bulky phosphine ligand in DMF. In contrast, use of a less polar solvent such as o-xylene is essential for the successive

4,5-diarylation of a thiazole substrate having 5-carboxanilide function as sacrificial group. These methods seem to be useful for preparing oligoaryl compounds having a thiazole unit.

3. Experimental

3.1. General

^{1}H and ^{13}C NMR spectra were recorded at 400 and 100 MHz, respectively, for $CDCl_3$ solutions unless otherwise noted. MS analysis was made by EI. GC analysis was carried out using a Silicone OV-17 glass column (i.d. 2.6 mm×1.5 m). 2-Phenylthiazole (**4**) was prepared according to a published procedure.[12] 2-Phenyl-5-thiazolecarboxanilide (**10**) and 2-phenyl-5-oxazolecarboxanilide (**12**) were prepared from 5-bromo-2-phenylthiazole[12] and 5-bromo-2-phenyloxazole[13] by a carbonylation method reported previously using aniline and $PdCl_2(PPh_3)_2$ as nucleophile and catalyst, respectively.[14] Amide **10**: Mp 219–220°C; ^{1}H NMR (DMSO-d_6) δ 7.14 (t, *J*=7.3 Hz, 1H), 7.39 (t, *J*=8.0 Hz, 2H), 7.54–7.56 (m, 3H), 7.73 (d, *J*=7.6 Hz, 2H), 8.02–8.45 (m, 2H), 8.69 (s, 1H), 10.47 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 120.62, 124.30, 126.71, 128.94, 129.57, 131.37, 132.68, 135.83, 138.52, 144.96, 158.62, 170.93; HRMS *m/z* (M^+) calcd for $C_{16}H_{12}N_2OS$ 280.0687, found 280.0665. Amide **12**: Mp 164.5–165°C; ^{1}H NMR δ 7.19 (t, *J*=7.3 Hz, 1H), 7.39 (t, *J*=7.8 Hz, 2H), 7.49–7.55 (m, 3H), 7.65–7.68 (m, 2H), 7.91 (s, 1H), 8.00 (s, 1H), 8.11–8.14 (m, 2H); ^{13}C NMR δ 120.31, 125.11, 126.31, 127.03, 129.01, 129.19, 131.63, 133.22, 136.81, 144.82, 154.90, 162.58; HRMS *m/z* (M^+) calcd for $C_{16}H_{12}N_2O_2$ 264.0899, found 264.0901. Other starting materials were commercially available. The solvents employed were purified by standard methods before use. The following experimental procedure may be regarded as typical in methodology and scale.

3.1.1. Reaction of thiazole (2) with 4-bromoanisole (1a). In a 100 cm^3 two-necked flask was placed Cs_2CO_3 (4.8 mmol, 1.56 g), which was then dried at 150°C in vacuo for 2 h. Then, $Pd(OAc)_2$ (0.1 mmol, 22.4 mg), P(*t*-Bu)$_3$ (0.2 mmol, 40.5 mg), **1a** (4.8 mmol, 898 mg), **2** (2 mmol, 170 mg), 1-methylnaphthalene (ca. 100 mg) as internal standard and DMF (5 cm^3) were added. The resulting mixture was stirred under N_2 at 150°C for 8 h. After cooling, the reaction mixture was extracted with ethyl acetate and dried over sodium sulfate. Column chromatography on silica gel using hexane–ethyl acetate (95:5) as eluent gave 2,5-di(4-anisyl)thiazole[2b,c] (**3a**) (410 mg, 69%): Mp 174–175°C; ^{1}H NMR δ 3.84 (s, 3H), 3.86 (s, 3H), 6.93–6.97 (m, 4H), 7.51 (d, *J*=8.7 Hz, 2H), 7.85–7.90 (m, 3H); ^{13}C NMR δ 55.37, 55.40, 114.29, 114.49, 124.17, 126.73, 127.73, 127.84, 137.88, 138.22, 159.63, 161.03, 166.24; MS *m/z* 297 (M^+). Anal. calcd for $C_{17}H_{15}NO_2S$: C, 68.66; H, 5.08; N, 4.71; S, 10.78. Found: C, 68.47; H, 5.10; N, 4.68; S, 10.41.

3.2. Products

Compounds **3b**,[5a] **7**,[15] **9a**,[16] **9b**,[5a] **9c**,[16] **11b**,[17] **11c**[18] and **13**[19] are known. The characterization data of new compounds are given below.

3.2.1. 2,5-Di(4-chrolophenyl)thiazole (3c). Mp 131–132°C; ^{1}H NMR δ 7.39 (d, *J*=8.3 Hz, 2H), 7.43 (d, *J*=8.7 Hz, 2H), 7.52 (d, *J*=8.3 Hz, 2H), 7.89 (d, *J*=8.7 Hz, 2H), 7.98 (1H, s); ^{13}C NMR δ 127.55, 127.82, 129.25, 129.35, 129.70, 131.98, 134.31, 136.13, 138.36, 139.57, 166.06; MS *m/z* 305, 307, 309 (M^+). Anal. calcd for $C_{15}H_9Cl_2NS$: C, 58.84; H, 2.96; N, 4.57. Found: C, 58.87; H, 3.04; N, 4.51.

3.2.2. 2,5-Di(1-naphthyl)thiazole (3d). Mp 122–123°C; ^{1}H NMR δ 7.53–7.68 (m, 7H), 7.92–7.98 (m, 5H), 8.11 (s, 1H), 8.27–8.30 (m, 1H), 8.98 (d, *J*=8.3 Hz, 1H); ^{13}C NMR δ 125.10, 125.32, 125.32, 125.94, 126.32, 126.41, 126.92, 127.40, 128.41, 128.53, 128.60, 128.64, 128.78, 129.28, 130.48, 130.57, 130.71, 131.91, 133.86, 134.12, 137.05, 142.47, 167.81; MS *m/z* 337 (M^+). Anal. calcd for $C_{23}H_{15}NS$: C, 81.87; H, 4.48; N, 4.15; S, 9.50. Found: C, 81.68; H, 4.67; N, 4.08; S, 9.39.

3.2.3. 2-(Isobutyl)-5-phenylthiazole (8). Oil; ^{1}H NMR δ 1.03 (d, *J*=6.8 Hz, 6H), 2.14 (m, 1H), 2.88 (d, *J*=7.3 Hz, 2H), 7.30 (t, *J*=7.3 Hz, 1H), 7.38 (dd, *J*=7.8, 7.3 Hz, 2H), 7.53 (d, *J*=7.8 Hz, 2H), 7.83 (s, 1H); ^{13}C NMR δ 22.30, 29.82, 42.57, 126.59, 127.95, 129.00, 131.69, 137.61, 138.46, 169.68; MS *m/z* 217 (M^+). Anal. calcd for $C_{13}H_{15}NS$: C, 71.85; H, 6.96; N, 6.44. Found: C, 71.81; H, 6.87; N, 6.17.

3.2.4. 4,5-Di(4-methoxyphenyl)-2-phenylthiazole (11a). Mp 122–123°C; ^{1}H NMR δ 3.81 (s, 3H), 3.83 (s, 3H), 6.83–6.89 (m, 4H), 7.32 (d, *J*=8.8 Hz, 2H), 7.40–7.46 (m, 3H), 7.55 (d, *J*=8.8 Hz, 2H), 7.98–8.00 (m, 2H); ^{13}C NMR δ 55.23, 55.29, 113.68, 114.18, 124.48, 126.33, 127.76, 128.84, 129.77, 130.27, 130.81, 131.74, 133.79, 150.05, 159.16, 159.50, 164.68; MS *m/z* 373 (M^+). Anal. calcd for $C_{23}H_{19}NO_2S$: C, 73.97; H, 5.13; N, 3.73, S, 8.59. Found: C, 73.91; H, 5.12; N, 3.71; S, 8.43.

3.2.5. 4,5-Di(1,1′-biphenyl-4-yl)-2-phenylthiazole (11e). Mp 194–195°C; ^{1}H NMR δ 7.34–7.38 (m, 2H), 7.41–7.50 (m, 7H), 7.52 (d, *J*=8.4 Hz, 2H), 7.57–7.64 (m, 8H), 7.74 (d, *J*=8.0 Hz, 2H), 8.04–8.06 (m, 2H); ^{13}C NMR δ 126.46, 126.97, 127.00, 127.00, 127.35, 127.40, 127.62, 128.76, 128.87, 128.93, 129.52, 129.97, 130.03, 131.04, 132.83, 133.63, 134.00, 140.22, 140.50, 140.69, 140.92, 150.52, 165.56; MS *m/z* 465 (M^+). Anal. calcd for $C_{33}H_{23}NS$: C, 85.13; H, 4.98; N, 3.01; S, 6.89. Found: C, 84.87; H, 5.05; N, 2.96; S, 6.77.

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