

HETEROCYCLES, Vol. 79, 2009, pp. 303 - 309. © The Japan Institute of Heterocyclic Chemistry
Received, 7th, July 2008, Accepted, 1st August, 2008, Published online, 4th August, 2008.
DOI: 10.3987/COM-08-S(D)3

PALLADIUM-CATALYZED ARYLATION AT C-H AND C-C BONDS OF MASKED THIAZOLE DERIVATIVES[‡]

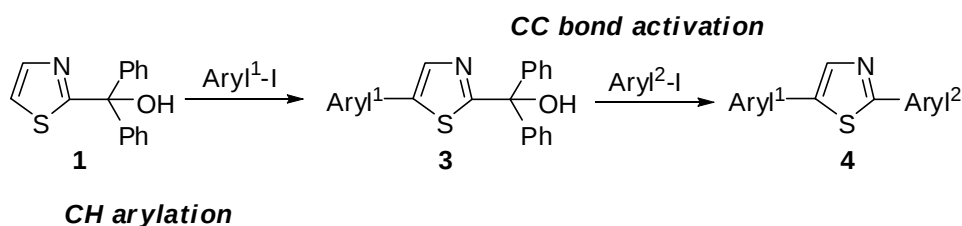
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[‡]To the memory of Dr. John Daly.

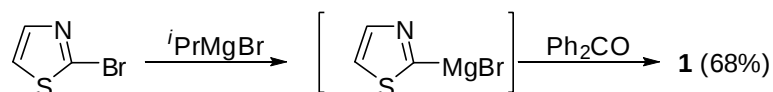
Abstract – The differently substituted 2,5-diarylthiazole derivatives are synthesized via palladium catalyzed sequential C–H arylation at the 5-position and C–C bond activation at the 2-position with masked thiazole.

Since 2,5-diarylated thiazoles show remarkable characteristics in photoluminescence, liquid crystal, and electrochemical redox, development of synthetic protocols for 2,5-diarylthiazoles is our major concern.¹ The cross-coupling methodology with a transition metal catalyst is a tool for the introduction of a substituent into the thiazole ring.² In particular, direct coupling of a thiazole derivative at the carbon–hydrogen bond by the catalysis of palladium is one of the practical way to introduce aryl and alkenyl groups via the carbon–carbon bond formation.^{3,4} We have reported that the C–H bond at the 2- and 5-positions of thiazole is efficiently substituted by various aryl groups with a palladium catalyst.⁵ Meanwhile, catalytic reactions via the cleavage of a C–C bond, in which a tertiary alcohol serves as a *masked* group of the corresponding C–H bond, have attracted much attention as a new class of transition metal-catalyzed carbon–carbon bond formation, and various catalytic processes involving different modes to activate the relatively inert bond have been developed.^{6,7} Our concern has thus focused on the use of such a reaction to the functionalization of thiazole derivatives. We herein describe that a new synthetic route to introduce an aryl moiety into thiazole at the 5-position and the 2-position with a thiazole derivative masked by a tertiary alcohol **1** via the C–H bond arylation and the arylation through C–C bond activation as shown in Scheme 1.



Scheme 1.

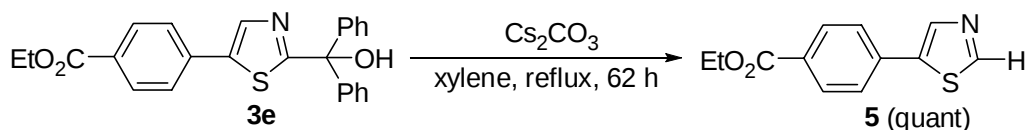
The masked thiazole **1** was prepared by the reaction of 2-bromothiazole with $i\text{PrMgBr}$ to form the intermediate Grignard reagent⁸ and following addition of benzophenone to afford the corresponding tertiary alcohol **1** in 68% yield. (Scheme 2)



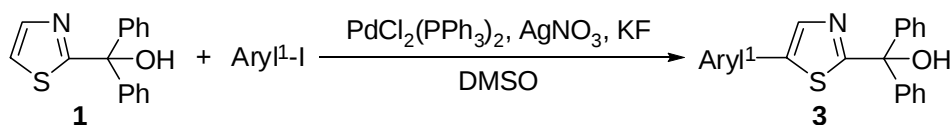
Scheme 2.

C–H arylation at the 5-position was first examined with masked thiazole **1** and an aryl iodide in the presence of a palladium catalyst and silver(I) nitrate/potassium fluoride as an activating agent. It was found to undergo the reaction affording the 5-arylated product. The reaction proceeded under similar conditions to those of 2-arylthiazole with an aryl iodide despite the presence of a hydroxy group in the molecule. Formation of the C–C bond at the 5-position of thiazole was found to occur.^{5b} Accordingly, the masked thiazole serves as a protective group in the palladium-catalyzed reaction. The reaction with other aryl iodides was examined as shown in Table 1. Iodobenzene and aryl iodides bearing an electron-donating substituent at the 4-position afforded **3** in 39–51% yields (entries 1–3). On the other hand, iodides bearing an electron-withdrawing substituent CF_3 (82%, entry 4) or CO_2Et (quant, entry 5) resulted in excellent yields.

Deprotection of the masked group was found to take place by treatment of **3e** with Cs_2CO_3 under reflux in xylene to afford the corresponding 5-arylated thiazole in a quantitative yield. (Scheme 3) Since few example on regioselective arylation at the 5-position of unsubstituted thiazole is reported,^{3b,3k} the method would be a practical surrogate for the direct 5-arylation.^{5b}



Scheme 3.

Table 1. Reaction with C–H arylation at the 5-position of **1**^a

Entry	Aryl ¹ -I	Product	Yield (%)
1	C ₆ H ₅ I (2a)	3a	39
2	4-MeOC ₆ H ₄ I (2b)	3b	40
3	4-MeC ₆ H ₄ I (2c)	3c	51
4	4-CF ₃ C ₆ H ₄ I (2d)	3d	82
5	4-EtOCOC ₆ H ₄ I (2e)	3e	quant

^a The reaction was carried out with **1** (0.5 mmol) and **2** (0.6 mmol) in the presence of 5 mol% of PdCl₂(PPh₃)₂, AgNO₃ (0.6 mmol) and KF (1.0 mmol) in DMSO (3 mL) at 100 °C for 5 h.

We then carried out the palladium-catalyzed reaction at the 2-position through the C–C bond activation in the presence of Cs₂CO₃ to undergo the 2-arylation (Table 2). The reaction of **3e** with various aryl halides **2** (Cl, Br, and I) was employed for the reaction to obtain **4a** to bring about similar yields (entry 1-3). It should be pointed out that aryl bromides and chlorides reacted similarly to aryl iodides when a bulky phosphine was employed as a ligand of palladium catalyst.^{7f,10} The masked thiazole bearing an electron-withdrawing substituent was found to undergo the reaction smoothly. Indeed, the reaction of **3e** proceeded with both electron-rich iodides **2a,b** and those having an electron-withdrawing substituent **2d-e** to give **4a-d**. The reaction of **3b**, which possesses electron-enriched aryl group as a substituent at the 5-position, with electron-deficient aryl iodide **2e** proceeded in a good yield (entry 7), while the reaction of electron-enriched **2b** resulted in a poor yield (entry 8).

With differently substituted 2,5-diarylthiazole **4b** and **4e** in hand, we then compared characteristics of these isomers. Figure 1 shows fluorescence spectra of the obtained 2,5-diarylthiazoles. Both compounds showed photoluminescence. The quantum yield of **4e** was found to be $\Phi = 0.56$, which was ca. twice higher than that of **4b** ($\Phi = 0.24$).

Table 2. Reaction at the 2-position through the C–C bond activation of **3** with aryl halide **2**

$$\begin{array}{c}
 \text{Pd(OAc)}_2, \\
 \text{P(biphenylene-2-yl)}(^t\text{Bu})_2, \\
 \text{Cs}_2\text{CO}_3 \\
 \xrightarrow{\text{xylene}}
 \end{array}$$

Entry	3	Aryl ² -X	Product	Time (h)	Yield (%)
1	3e	C ₆ H ₅ Cl (2f)	4a	33	49 ^a
2	3e	C ₆ H ₅ Br (2g)	4a	11	66 ^a
3	3e	C ₆ H ₅ I (2a)	4a	11	55 ^a
4	3e	4-MeOC ₆ H ₄ I (2b)	4b	22	61 ^a
5	3e	4-CF ₃ C ₆ H ₄ I (2d)	4c	15	45 ^b
6	3e	4-EtOCOC ₆ H ₄ I (2e)	4d	80	48 ^b
7	3b	2e	4e	60	54 ^a
8	3b	2b	4f	12	15 ^a

^a The reaction was carried out with **3** (0.1 mmol) and **2** (0.12 mmol) in the presence of 5 mol% of Pd(OAc)₂, 10 mol% of P(biphenylene-2-yl)(^tBu)₂ and Cs₂CO₃ in xylene (1.6 mL) at 150 °C. ^b CuI (10 mol%) was used as a cocatalyst. PPh₃ was employed in place of P(biphenylene-2-yl)(^tBu)₂.

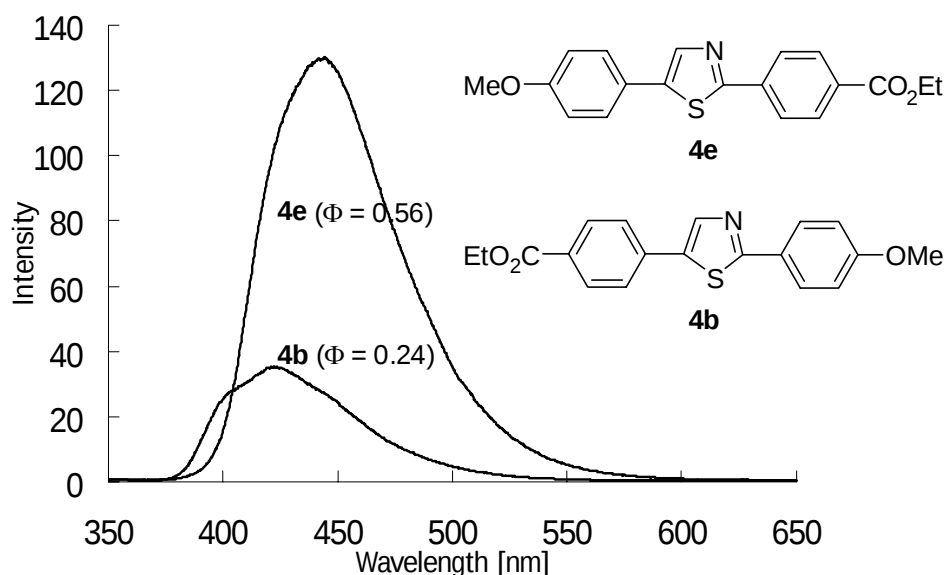


Figure 1. Fluorescence spectra of **4b** and **4e** as 1×10^{-5} and 1×10^{-6} M solutions of chloroform, respectively.

In summary, we showed that palladium-catalyzed arylation reactions of masked thiazole took place at the C–H bond of the 5-position of thiazole and at the C–C bond of the 2-position. The masked group was found to serve as a functional group to promote C–C bond formation via C–C bond activation at the 2-position of thiazole, as well as a protective group in the 5-arylation reaction with a palladium catalyst

and a silver salt. The protocols allow the introduction of the substituent in an opposite order, which reacts at the 5-position and then at the 2-position, to our conventional 2-arylation and the following 5-arylation sequence.¹⁰

ACKNOWLEDGEMENT

This work was partially supported by a Grant-in-Aid for Scientific Research on Priority Areas, "Advanced Molecular Transformation of Carbon Resources" by Ministry of Education, Culture, Sports, Science and Technology (MEXT), Japan.

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10. **Arylation of **3e** at the 2-position through the C–C bond activation with **2e** (Table 2, Entry 6)** To a 25 mL Schlenk tube equipped with a magnetic stirring bar were added Cs₂CO₃ (39.1 mg, 0.12 mmol), Pd(OAc)₂ (1.42 mg, 0.005 mmol), P(biphenylene-2-yl)(^tBu)₂ (2.98 mg, 0.01 mmol), xylene (1.6 mL), ethyl 4-iodobenzoate **2e** (33 mg, 20 μ L, 0.12 mmol), and **3e** (41.6 mg, 0.1 mmol). The reaction mixture was stirred at 150 °C under N₂ atmosphere for 80 h. After cooling to rt, the mixture was poured onto saturated aqueous NH₄Cl and extracted with EtOAc. The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated under reduced pressure to leave a crude solid, which was purified by chromatography on silica gel to afford 18.3 mg of **4d** (48%).^{5a}