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USE OF NaOH AS A NEW ACTIVATOR FOR THE PALLADIUM-CATALYZED DIRECT CH ARYLATION OF THIAZOLE DERIVATIVES‡

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‡This paper is dedicated to Professor Emeritus Keiichiro Fukumoto on the occasion of his 75th birthday.

Abstract – Sodium hydroxide is found to serve as a new activator for the palladium-catalyzed C-H arylation of thiazole derivatives with aryl bromides and aryl iodides. The reaction of benzothiazole proceeds smoothly with 4-bromoanisole to afford the corresponding coupling product in an excellent yield.

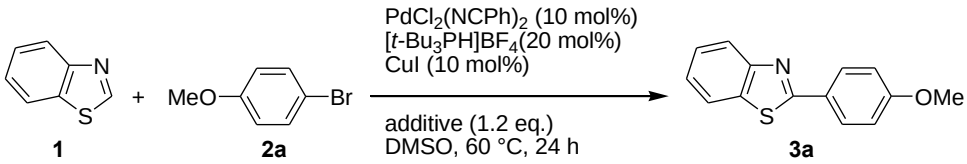
Thiazole, which is a five-membered heteroaromatic compound composed of nitrogen and sulfur atom, shows remarkable properties as functional organic materials as well as biologically important molecules.[1] Synthesis of substituted thiazole derivatives is thereby a major concern in synthetic organic chemistry. The cross-coupling methodology with a transition metal catalyst is a practical 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 recently shown that the reaction of thiazole with an aryl iodide with a palladium/copper catalyst system in the presence of tetrabutylammonium fluoride (TBAF) as an activator induces carbon–carbon bond formation at the 2-position of thiazole.[5] The reaction was found to take place under mild conditions when several aryl iodies are employed as an organic electrophile, while use of aryl bromides was found to result in no reaction. Since the use of bromides as an electrophile for the coupling reaction considerably extends synthetic utility, our further concern has centered to investigate new catalytic reaction system to allow the reaction of aryl bromides for the introduction of the substituent into thiazole. We herein report that the use of sodium hydroxide as an activator undergoes the direct CH arylation of thiazole derivatives with aryl bromides when bulky trialkylphosphine is employed as a ligand for the palladium catalyst.[6]

We have examined the reaction of thiazole with 4-bromoanisole under the reaction conditions for aryl iodides using TBAF[5a] to result in no reaction. Switching the ligand of palladium to (t-Bu_3)P was also ineffective. However, the reaction was found to occur when an inorganic base such as potassium carbonate and sodium hydroxide is employed instead of TBAF.

When the reaction of benzothiazole **1** (0.5 mmol) with 4-bromoanisole **2a** (0.6 mmol) was carried out with $PdCl_2(NCPh)_2$ (10 mol%)-[t-Bu_3PH]BF_4 (20 mol%)/CuI (10 mol%) and sodium hydroxide (0.6 mmol) in 3 mL of DMSO, the CH arylation reaction to give the coupling product **3a** was obtained in 66% yield after stirring at 60 ºC for 24 h (entry 1). Results on the reaction of **1** and **2a** under several conditions are summarized in Table 1. Longer reaction period to 46 h improved the yield to 82% (entry 2). Use of aqueous solution of NaOH (1M) did not undergo the reaction at all (entry 3). By contrast, use of the aqueous solution of K_2CO_3 afforded **3a** in moderate yields (entry 4), while the reaction with anhydrous K_2CO_3 was found to be ineffective (entry 5). The reaction with tricyclohexylphosphine as a ligand for the palladium catalyst resulted in lower yield (11%, entry 5) and attempted another phosphine ligands have been completely ineffective so far.

Table 1. C-H arylation of benzothiazole **1** with 4-bromoanisole **2a**[a]

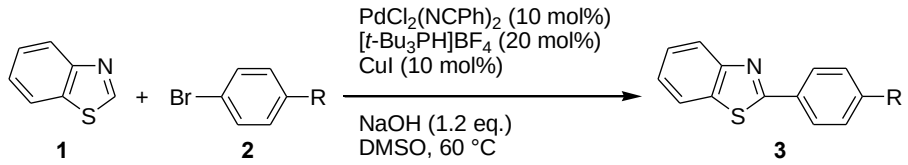


Entry	Additive	Yield (%)
1	NaOH	66
2[b]	NaOH	82
3	1 M aq. NaOH	0
4	1 M aq. K_2CO_3	36
5	K_2CO_3	11
6[c]	NaOH	11

[a] The reaction was carried out with **1** (0.5 mmol) and **2** (0.6 mmol) in the presence of 10 mol% of $PdCl_2(NCPh)_2$, 20 mol% of [t-Bu_3PH]BF_4 and 10 mol% of CuI in DMSO (3 mL) with the additive (0.6 mmol) at 60 ºC. [b] Reaction time was extended to 46 h. [c] PCy_3 was employed in place of [t-Bu_3PH]BF_4.

The reaction with other aryl bromides were examined as shown in Table 2. Bromides bearing an electron-donating substituents such as Me, NMe_2 afforded **3** in good yields. On the other hand, the reaction of methyl 4-bromobenzoate resulted in a poor yield (18%).

Table 2. Reaction with various aryl bromides **2**[a]

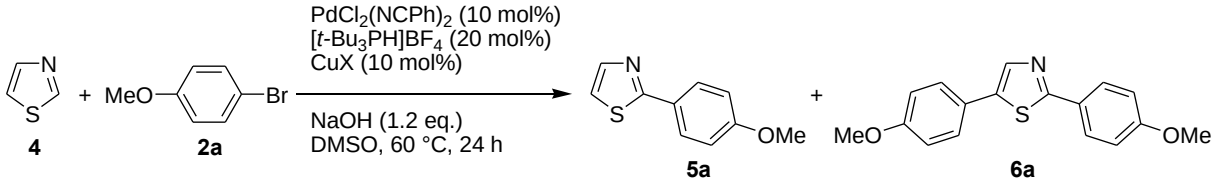


Entry	R	Time (h)	Yield (%)
1	Me	48	88
2	H	48	81
3	NMe_2	24	91
4	CO_2Me	72	18

[a] The reaction was carried out under the similar conditions to those for the entry 2 of Table 1.

The reaction of unsubstituted thiazole **4** was examined under the conditions with NaOH as an activator. Although the reaction of **4** with TBAF has been highly selective to take place at the 2-position to give **5a** and only a trace amount of 2,5-diarylated **6a** was furnished,[5a] the reaction with NaOH was found to be less selective to afford 37% of **5a** and 22% of **6a**. However, the improved selectivity was observed when the copper cocatalyst was switched to CuBr or CuCN. These results are summarized in Table 3.

Table 3. Reaction of thiazole **4**[a]

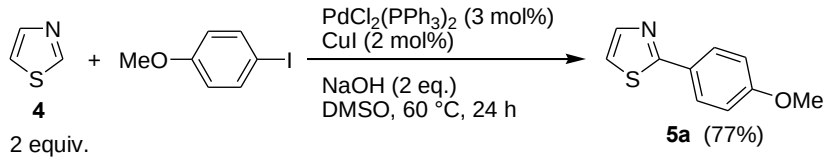


Entry	Additive	CuX	Yield (%)	
			5a	**6a**
1[b]	TBAF	CuI	82	6
2	NaOH	CuI	37	22
3	NaOH	CuBr	43	trace
4	NaOH	CuCN	64	trace

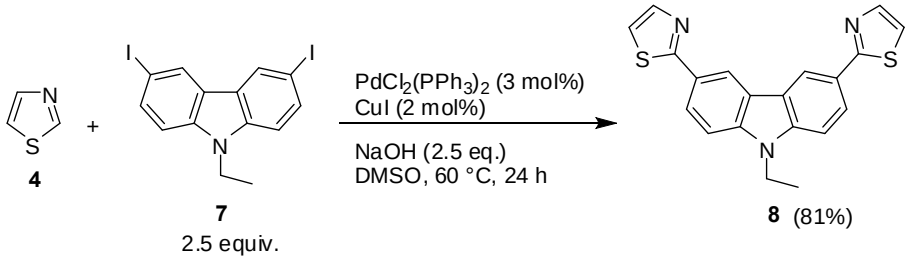
[a] The reaction was carried out under the similar conditions shown in Table 1 except the ratio of the substrates (**4**/**2a** = 2:1). [b]The reaction was performed with $PdCl_2(PPh_3)_2$ usder the conditions of ref 5a with 4-iodoanisole in place of **2a**.

The use of NaOH as an activator for the reaction of thiazole derivatives with aryl iodides was effective. Triphenylphosphine complex of palladium, $PdCl_2(PPh_3)_2$ was available for the reaction. When the

reaction of thiazole with 4-iodoanisole in the presence of $PdCl_2(PPh_3)_2$ (3 mol%)/CuI (2 mol%) and NaOH (2 equiv) was carried out in DMSO at 60 ºC, **5a** was obtained in 77% yield after stirring for 24 h. (eq 1-a) The reaction was also found to be applicable for the reaction of bifunctional aryl iodide **7** and thiazole to give **8**, which is potentially available for the preparation of photoluminescent materials. Several spectroscopic and electrochemical properties of **7** and the further derivatives will be described in due course.



eq. 1-a



eq 1-b

In summary, we have shown that sodium hydroxide is a new class of activator for the CH arylation reaction of thiazole derivatives. The availability of NaOH would extend synthetic usefulness of the CH arylation reaction of thiazoles, since NaOH shows advantage in the cost of synthesis toward TBAF. It is also worthy of note that aryl bromides are available for the reaction although further improvement of the catalytic reaction conditions is necessary.

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