

HETEROCYCLES, Vol. 83, No. 6, 2011, pp. 1371 - 1376. © The Japan Institute of Heterocyclic Chemistry
Received, 15th February, 2011, Accepted, 28th March, 2011, Published online, 14th April, 2011
DOI: 10.3987/COM-11-12176

AN EFFICIENT ARYLATION OF BENZOAZOLES WITH ARYL BROMIDES BY A PRACTICAL PALLADIUM-COPPER COCATALYTIC SYSTEM

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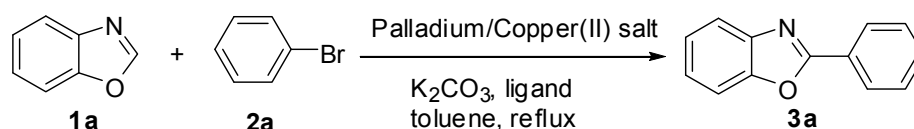
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Abstract – A practical, efficient Pd(OAc)₂/Cu(II)/PPh₃ cocatalytic system has been developed. With only 1 mol% Pd(OAc)₂, 20 mol% copper(II) salt, and 0.5 equiv of inexpensive PPh₃ as ligand, the direct arylation of benzoazoles with aryl bromides could be performed smoothly in mild condition, affording the desired arylated benzoazoles in good yields (75-93%).

Arylated azoles are ubiquitous in natural products and pharmaceuticals, agrochemicals.¹ The transition-metal catalyzed direct arylation of azoles is a powerful strategy for the synthesis of arylated azoles, and has recently received much attentions.² In this rapidly growing field, the direct cross-coupling between azoles and aryl halides is a main protocol.² As one of the most common arylated azoles, arylated benzoazoles have many biologically important activities.³ In most cases, the direct arylation of benzoazoles catalyzed by transition-metal required more reactive aryl iodides as arylating reagents.^{2b-d} The direct arylation of benzoazoles using aryl bromides, which are cheaper and more commonly used than aryl iodides, did not studied so widely as that using aryl iodides.^{4,5} In 2005, Alagille et al disclosed a Pd(OAc)₂/Cu(I)Br/P(*t*-Bu)₃ cocatalytic system for the direct arylation of benzoazoles with aryl bromides, affording arylated benzoazoles in 8-84% yields.^{5a} Very recently, Huang et al^{5b} developed an arylation of benzoazoles with aryl bromides by a palladium-copper cocatalytic system, which employed a complicated cocatalytic system: dichlorobis(chloro-di-*tert*-butylphosphine)/Cu(Xantphos)I. Herein we wish to report our recent work on the efficient arylation of benzoazoles with aryl bromides by a practical Pd(OAc)₂/Cu(II)/PPh₃ cocatalytic system.

The direct coupling of benzoxazole **1a** with bromobenzene **2a** using K_2CO_3 as a base in toluene was chosen as a model reaction. Initially, various copper salts and $Pd(OAc)_2$ with various N- and P-ligands were probed. It was found that N-ligands such as 1,10-phenanthroline or 2,2-bipyridine led to no desired coupling product (Table 1, entry 1). To our delight, when the inexpensive PPh_3 was used, the coupling reaction performed smoothly with only 1 mol% $Pd(OAc)_2$ and 20 mol% copper (II) salt such as $Cu(OAc)_2 \cdot H_2O$ and $CuCl_2 \cdot 2H_2O$ under air, affording the desired arylated benzoxazole **3a** in good yields (Table 1, entries 2 and 3). In the presence of other P-ligands such as $(n-Bu)_3P$ and bisdiphenylphosphinopropane (DPPP), good yields were also obtained (Table 1, entries 5-8). In contrast, no reaction proceeded in the absence of P-ligands (Table 1, entry 9). The screening of bases revealed that K_2CO_3 was much better than other bases for the reaction (Table 1, entries 10-12). Other palladium catalyst such as $PdCl_2$, $Pd(PPh_3)_4$, $Pd(PPh_3)_2Cl_2$, and $Pd(dba)_2$ with copper (II) salts can also give the desired product **3a** in good yields (Table 1, entries 13-17). Notably, if either copper or palladium catalyst was present, no arylated product **3a** was obtained under the above standard conditions (Table 1, entries 18, 19).

Table 1. Optimization of Direct Arylation of Benzoxazole^a

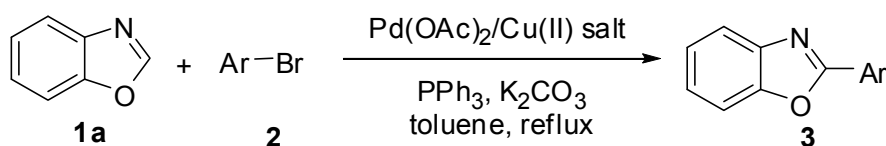


Entry	Copper	Palladium	Ligand	Yield ^b
1	Cu(II) salt ^c	$Pd(OAc)_2$	N-ligands ^d	0
2	$CuCl_2 \cdot 2H_2O$	$Pd(OAc)_2$	PPh_3	90
3	$Cu(OAc)_2 \cdot H_2O$	$Pd(OAc)_2$	PPh_3	92
4	$Cu(acac)_2$	$Pd(OAc)_2$	PPh_3	0
5	$CuCl_2 \cdot 2H_2O$	$Pd(OAc)_2$	$(n-Bu)_3P$	88
6	$Cu(OAc)_2 \cdot H_2O$	$Pd(OAc)_2$	$(n-Bu)_3P$	85
7	$CuCl_2 \cdot 2H_2O$	$Pd(OAc)_2$	DPPP	87
8	$Cu(OAc)_2 \cdot H_2O$	$Pd(OAc)_2$	DPPP	89
9	Cu(II) salt ^c	Palladium catalyst ^e	-	0
10 ^e	$CuCl_2 \cdot 2H_2O$	$Pd(OAc)_2$	PPh_3	0
11 ^e	$Cu(OAc)_2 \cdot H_2O$	$Pd(OAc)_2$	PPh_3	80
12 ^f	$CuCl_2 \cdot 2H_2O$	$Pd(OAc)_2$	PPh_3	70
13	$CuCl_2 \cdot 2H_2O$	$PdCl_2$	PPh_3	90
14	$Cu(OAc)_2 \cdot H_2O$	$PdCl_2$	PPh_3	87
15	$Cu(OAc)_2 \cdot H_2O$	$Pd(PPh_3)_2Cl_2$	PPh_3	90
16	$Cu(OAc)_2 \cdot H_2O$	$Pd(PPh_3)_4$	PPh_3	92
17	$Cu(OAc)_2 \cdot H_2O$	$Pd(dba)_2$	PPh_3	86
18	Cu(II) salt ^c	-	PPh_3	0
19	-	PdX^g	PPh_3	0

^aThe mixture of **1a** (1.0 mmol), **2a** (1.2 mmol), palladium catalyst (1.0 mol%), copper catalyst (20 mol%), ligand (0.5 equiv), and K_2CO_3 (2.0 equiv) in toluene (3 mL) was refluxed for 3 h under air. ^bIsolated yields(%). ^cCu(II) salt: $Cu(OAc)_2 \cdot H_2O$, $CuCl_2 \cdot 2H_2O$ et al. ^dN-ligands = 1,10-phenanthroline or 2,2-bipyridine. ^e CS_2CO_3 was used as base. ^f $K_3PO_4 \cdot 3H_2O$ was used as base. ^gPalladium catalysts listed in the table.

After screening of various copper and palladium catalysts, ligands, bases etc, it can be concluded that the optimized reaction should be performed by the cocatalytic system of 1 mol% Pd(OAc)₂ and 20 mol% Cu(OAc)₂·H₂O or CuCl₂·2H₂O in the presence of PPh₃ (0.5 equiv) and K₂CO₃ (2.0 equiv). Under the optimal reaction conditions, a series of aryl bromides **2a-i** were examined in the coupling reaction. It was found that the aryl bromides bearing either electron-donating or withdrawing groups on benzene rings **2a-i** could perform the coupling reaction smoothly with benzoxazole **1a** under air, furnishing the desired arylated benzoxazole **3a-i** in good yields (Table 2, compare entries 1-10). Heteroaryl bromides **2k-l** were also good coupling partners, giving the biheteroarenes **3k-l** in good yields (Table 2, entries 11, 12).

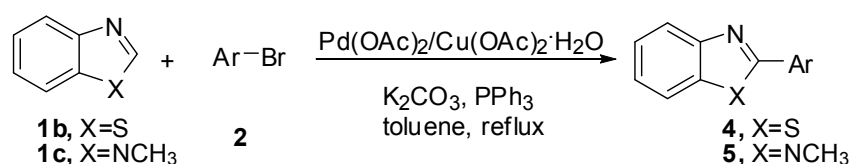
Table 2. Direct Arylation of Benzoxazole **1a** with Aryl Bromides **2**^a



Entry	Ar	Product 3 ^b	Yield (%) ^c	Yield (%) ^d
1	C ₆ H ₅	3a ^{7a}	93	92
2	4-MeOC ₆ H ₄	3b ^{7b}	88	91
3	3-MeOC ₆ H ₄	3c ^{7b}	90	89
4	4-MeC ₆ H ₄	3d ^{7c}	92	86
5	3-MeC ₆ H ₄	3e ^{7c}	84	89
6	3,5-Me ₂ C ₆ H ₃	3f ^{7b}	91	88
7	2-MeOC ₆ H ₄	3g ^{7b}	81	80
8	4-FC ₆ H ₄	3h ^{7a}	83	82
9	4-ClC ₆ H ₄	3i ^{7a}	87	83
10	naphthalen-1-yl	3j ^{7b}	83	85
11	pyridin-3-yl	3k ^{7b}	80	84
12	pyridin-2-yl	3l ^{7b}	80	77

^aThe mixture of **1a** (1.0 mmol), **2** (1.2 mmol), Pd(OAc)₂ (1.0 mol%), copper (II) salt (20 mol%), PPh₃ (0.5 equiv), and K₂CO₃ (2.0 equiv) in toluene (3 mL) was refluxed for 3 h under air. ^bIsolated yields. ^cCu(OAc)₂·H₂O was used as cocatalyst. ^dCuCl₂·2H₂O was used as cocatalyst.

Table 3. Direct Arylation of Benzothiazoles **1b** or Benzoimidazoles **1c** with Aryl Bromides **2**^a



Product	Ar	Yield (%) ^b	Product	Ar	Yield (%) ^b
4a ^{5b}	C ₆ H ₅	86	4i ^{4c}	pyridin-3-yl	79
4b ^{4c}	4-MeOC ₆ H ₄	92	5a ^{7b}	C ₆ H ₅	80
4c ^{4c}	3-MeOC ₆ H ₄	83	5b ^{7a}	4-MeOC ₆ H ₄	85
4d ^{5b}	4-MeC ₆ H ₄	84	5c ^{7b}	3-MeOC ₆ H ₄	81
4e ^{5b}	3-MeC ₆ H ₄	82	5d ^{7a}	4-MeC ₆ H ₄	83
4f ^{5b}	3,5-Me ₂ C ₆ H ₃	92	5e ^{7a}	3-MeC ₆ H ₄	77 ^c
4g ^{5b}	4-FC ₆ H ₄	81	5f ^{7a}	3,5-Me ₂ C ₆ H ₃	75
4h ^{4c}	naphthalen-1-yl	77	-	-	-

^aThe mixture of **1b** or **1c** (1.0 mmol), **2** (1.2 mmol), Pd(OAc)₂ (1.0 mol%), Cu(OAc)₂·H₂O (20 mol%), PPh₃ (0.5 equiv), and K₂CO₃ (2.0 equiv) in toluene (3 mL) was refluxed for **1b** 6 h or for **1c** 10 h.

^bIsolated yields. ^cCuCl₂·2H₂O was used as cocatalyst.

Moreover, benzothiazole **1b** and benzoimidazole **1c** were also tested in the coupling reaction using Pd(OAc)₂/Cu(OAc)₂·H₂O/PPh₃ as a cocatalytic system. It was found that both benzothiazole **1b** and benzoimidazole **1c** could react smoothly with various aryl bromides **2** to give the desired arylated products **4** and **5** in moderate to good yields (Table 3). Compared with benzoxazole **1a**, benzothiazole **1b** and benzoimidazole **1c** were less reactive and required longer reaction time (3 h for **1a**, 6 h for **1b** and 10h for **1c**), probably because the acidities of H-2 in **1b** and **1c** are weaker than that in **1a**.⁶

In summary, a practical Pd(OAc)₂/Cu(II)/PPh₃ cocatalytic system has been developed for the direct arylation of benzoazoles **1a**, benzothiazole **1b** or benzoimidazole **1c** with various aryl bromides **2**. The yields (75-93%) are better than that using Pd(OAc)₂/Cu(I)Br/ P(*t*-Bu)₃.^{5a} This synthetic reaction also has the advantages of readily available catalysts, low palladium catalyst loading, mild reaction conditions, and simple manipulations.

EXPERIMENTAL

General procedure for the arylation of benzoazoles **1a-c** with aryl bromide **2**: The reaction mixture of benzoazoles **1a-c** (1.0 mmol), aryl bromide **2** (1.2 mmol), Pd(OAc)₂ (2.2 mg, 1.0 mol%), Cu(OAc)₂·H₂O or CuCl₂·2H₂O (20 mol%), and K₂CO₃ (2.0 equiv, 0.276 g) in toluene (3 mL) was refluxed for 3-10 h. Then, the mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was purified by column chromatography (silica gel, petroleum ether/ EtOAc as eluent) to give arylated benzoxazole **3-5** (All the coupling products **3a**^{7a}, **b**^{7b}, **c**^{7b}, **d**^{7c}, **e**^{7c}, **f**^{7b}, **g**^{7b}, **h**^{7a}, **i**^{7a}, **j**^{7b}, **k**^{7b}, **l**^{7b}; **4a**^{5b}, **b**^{4c}, **c**^{4c}, **d**^{5b}, **e**^{5b}, **f**^{5b}, **g**^{5b}, **h**^{4c}, **i**^{4c}; **5a**^{7b}, **b**^{7a}, **c**^{7b}, **d**^{7a}, **e**^{7a}, **f**^{7a} are known compounds).

ACKNOWLEDGEMENTS

Financial supports from National Natural Science Foundation of China (No. 20872059 and 21072091) and MOST of China (973 program 2011CB808600) are gratefully acknowledged.

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