Palladium-Catalyzed C–H Cyclization in Water: A Milder Route to 2-Arylbenzothiazoles

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Abstract: Water was successfully employed as a reaction medium in palladium-catalyzed C–H cyclization of thiobenzanilides. Reactions efficiently proceeded under considerably mild conditions such as 40 °C in water, providing a more practical, greener method for the synthesis of 2-arylbenzothiazoles. For some substrates, the addition of an amphiphilic surfactant greatly enhanced the process. The method represents a rare example of palladium-catalyzed C–H functionalization processes performed in water.

Key words: palladium, catalysis, heterocycles, water, C-H functionalization

The use of water as a solvent for organic synthesis has recently attracted considerable attention because it offers a range of advantages such as inexpensiveness, wide availability, nontoxicity, and nonflammability, thus providing highly economic and sustainable synthetic routes.¹ While its use is sometimes hampered by the insolubility of the polar organic molecules, the addition of an amphiphilic surfactant, forming micelles, has been known to have a positive effect for the reactions conducted in water, resulting from hydrophobic and concentration effects in the microheterogeneous two-phase system.²

Considerable progress has been made in the development of novel transformations via transition-metal-catalyzed C–H functionalization recently. A wide range of catalytic systems, which successfully effect carbon-carbon and carbon-heteroatom bond-forming reactions, have so far been developed.³ Very recently, our group reported a versatile synthetic method for preparing 2-arylbenzothiazoles involving a palladium-catalyzed C-H functionalization-intramolecular C-S formation process.⁴ Indeed, this represents a rare example of C-S formation through transition-metal-catalyzed C-H functionalization.⁵ Although variously substituted 2-arylbenzothiazoles can be obtained by using the method, the process requires harsh reaction conditions in terms of high temperatures (100– 120 °C); therefore, the development of a milder approach for synthesizing benzothiazoles is still of considerable importance from a point of view of applicability.

Herein, we describe our finding that palladium-catalyzed C–H cyclization of thiobenzanilides can be successfully performed in water by carefully tuning the catalytic system. For some substrates, it was found that the addition of

SYNLETT 2012, 23, 1678–1682 Advanced online publication: 13.06.2012 DOI: 10.1055/s-0031-1291164; Art ID: ST-2012-U0182-L © Georg Thieme Verlag Stuttgart · New York an amphiphilic surfactant greatly enhanced the cyclization process.⁶ Compared to the previously reported methods,⁴ the reactions efficiently proceeded under considerably milder conditions (40 °C vs. 100–120 °C) in water, thus resulting in a more practical, greener synthesis of benzothiazoles.^{7–9}

Table 1 Effect of Reaction Parameters^a

	N Ph	"Pd" cat. (x mol%) Base (1 equiv)		-N		
	В Н 1а	H ₂ O, 40 °C, 24 h O ₂ (1 atm)	S 2a			
Entry	Pd catalyst (1	nol%)	Base	Yield (%)		
1	$PdCl_2(10)$		CsF	0		
2	$PdCl_{2}(10) +$	TMEDA (10)	CsF	0		
3	$PdCl_{2}(10) +$	bipyridyl (10)	CsF	0		
4	$PdCl_{2}(10) +$	proline (10)	CsF	0		
5	PEPPSI-IPr ((10)	CsF	0		
6	$PdCl_{2}(10) +$	t-Bu ₃ P·HBF ₄ (10)	CsF	0		
7	$PdCl_{2}(10) +$	DPEPhos (10)	CsF	0		
8	$PdCl_{2}(10) +$	Ph ₃ P (20)	CsF	14		
9	$PdCl_{2}(10) +$	$P(2-Tol)_3(20)$	CsF	54		
10	$PdCl_{2}(10) +$	$P(2-Tol)_3(20)$	KF	21		
11	$PdCl_{2}(10) +$	$P(2-Tol)_3(20)$	NaOMe	53		
12	$PdCl_{2}(10) +$	$P(2-Tol)_3(20)$	K ₂ CO ₃	54		
13	$PdCl_{2}(10) +$	$P(2-Tol)_3(20)$	Rb ₂ CO ₃	63		
14	$PdBr_{2}(10) +$	P(2-Tol) ₃ (20)	Rb ₂ CO ₃	63		
15	$Pd(OAc)_2$ (10)	$P(2-Tol)_3(20)$	Rb ₂ CO ₃	55		
16	$Pd(acac)_2$ (10	$P(2-Tol)_{3}(20)$	Rb ₂ CO ₃	47		
17	$Pd_2(dba)_3(5)$	$+ P(2-Tol)_3 (20)$	Rb ₂ CO ₃	83		
18 ^c	$Pd_{2}(dba)_{3}(5)$	+ P(2-Tol) ₃ (20)	Rb ₂ CO ₃	64		
19 ^d	$Pd_{2}(dba)_{3}(5)$	$+ P(2-Tol)_{3}(20)$	Rb ₂ CO ₃	13		

^a Reaction was run on a 0.15 mmol scale in H₂O (3 mL).

^b Isolated yield.

^c Under an air atmosphere.

^d Performed at r.t.

We began our investigation using thiobenzanilide (1a) to identify the optimal reaction conditions that would produce the desired product 2a in water (Table 1). On the basis of our recent report,^{4b} the reaction of **1a** in water was first carried out in the presence of 10 mol% of PdCl₂ and one equivalent of CsF at 40 °C under an O₂ atmosphere. However, no desired benzothiazole 2a was obtained (Table 1, entry 1). Thus, the effect of a ligand was next evaluated (Table 1, entries 2-9). A range of ligands, including diamines, amino acids, NHC, and phosphines, were tested, and it was found that 2a was obtained only when a monodentate arylphosphine was employed for the process (Table 1, entries 8 and 9). Among them, P(2-Tol)₃ gave the best result, giving rise to 2a in 54% yield (Table 1, entry 9). A subsequent screening of base (Table 1, entries 10–13) revealed that the use of Rb_2CO_3 gave a slightly better result (Table 1, entry 13). Examination of the optimal palladium source (Table 1, entries 14-17) resulted in the finding that the use of Pd(0) such as $Pd_2(dba)_3$ provided 2a in high yield (Table 1, entry 17). The reaction carried out under an air atmosphere gave a somewhat lower yield, suggesting that O₂ efficiently worked as an oxidant for the process (Table 1, entry 18). Unfortunately, the reaction performed at room temperature resulted in a formation of **2a** only in 13% yield (Table 1, entry 19).

The scope of the catalytic conditions developed above was next evaluated using variously substituted thiobenzanilides (Table 2). Whereas substrates **1b–d,o,p**, which contain an electron-donating methoxy or methyl group on the benzene ring, showed good reactivity (Table 2, entries 2–4, 15, and 16), the reactions of substrates possessing an

> Pd₂(dba)₃ (5 mol%) P(2-Tol)₃ (20 mol%)

electron-withdrawing group afforded the cyclized products 2e-n,q-s generally in lower yields (Table 2, entries 5-14 and 17-19, conditions A). However, further examination of the reaction conditions revealed that the addition of a surfactant such as Triton X-100 greatly enhances the process (Table 2, entries 5–14 and 17–19, conditions B).¹⁰ In this benzothiazole synthesis, yields are generally high and are comparable to those from previously established methods.⁴ Good functional-group compatibility (e.g., cyano, alkoxycarbonyl) is also observed. It is particularly noteworthy that the whole range of halogen atoms, including iodine, can be incorporated (Table 2, entries 9–13). Moreover, substrates possessing a heteroaromatic ring system (1t and 1u) were found to be suitable for the process although the yields were moderate (Table 2, entries 20 and 21).¹¹

In conclusion, we have demonstrated that the Pd-catalyzed C–H cyclization of thiobenzanilides can be successfully performed in water. For reactions of some substrates, the addition of an amphiphilic surfactant greatly improved the yields. Variously substituted 2-arylbenzothiazoles were efficiently obtained generally in high yields under considerably mild conditions (40 °C) in water, which compares favorably with the previously reported methods (100–120 °C in high-boiling solvents such as DMSO and NMP).⁴ Indeed, this method represents a rare example of Pd-catalyzed C–H functionalization processes in water.⁷ Further investigations into the use of water as a reaction medium in other Pd-catalyzed C–H functionalization processes are under way.

Ar ¹	S H 1	Rb ₂ CO ₃ (1 equiv) H ₂ O [Triton X-100 (30 mol%)] 40 °C, 24 h O ₂ (1 atm)	Ar ¹	r^{N} Ar ² S			
Entry	Substrate		1	Product	2	Yield (%) ^b for conditions A ^c	Yield (%) ^b for conditions B ^c
1	H H	S	1a		2a	83	-
2	мео	HN S	1b	MeO	2b	80	-
3	MeO	H H H	1c	MeO	2c	90	-

 Table 2
 Substrate Scope of the Process^a

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 Table 2
 Substrate Scope of the Process^a (continued)



Entry	Substrate	1	Product	2	Yield (%) ^b for conditions A ^c	Yield (%) ^b for conditions B ^c
4	H H H H S	1d		2d	quant.	_
5 ¹²	D ₂ N H S	1e	O ₂ N S	2e	10	77
6	NC H S	1f	NC S	2f	18	74
7	NC H S	1g		2g	21	61
8	EtO ₂ C H S	1h	EtO ₂ C	2h	15	84
9	CI H S	1i		2i	55	83
10	Br H S	1j	Br	2j	30	82
11	Br H S	1k	Br	2k	27	86
12	H S	11		21	14	70
13	F H H H S	1m	F S S	2m	62	75

 Table 2
 Substrate Scope of the Process^a (continued)



Entry	Substrate	1	Product	2	Yield (%) ^b for conditions A ^c	Yield (%) ^b for conditions B ^c
14	Ph H H H S	1n	Ph N S	2n	62	87
15	H H S	10		20	76	-
16	H H S OMe	1p		2p	86	-
17	H H S	1q		2q	38	68
18	H H S	1r		2r	59	64
19	NC H S	1s	NC S OMe	28	19	70
20	H H H H	1t		2t	17	44
21	S H S	1u	s s	2u	29	69

 $^{\rm a}$ Reaction was run on a 0.15 mmol scale in $\rm H_2O$ (3 mL).

^b Isolated yield.

^c Conditions A: without Triton X-100; conditions B: with Triton X-100.

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- (11) (a) As preliminary mechanistic studies, reactions using the isotopically labeled substrates were carried out, which resulted in the observation of KIEs (kinetic isotope effects) of 2.3–2.7. For details, see Supporting Information. (b) For C–S bond-forming reductive elimination from Pd(IV) complexes, see: Zhao, X.; Dong, V. M. Angew. Chem. Int. Ed. 2011, 50, 932.
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