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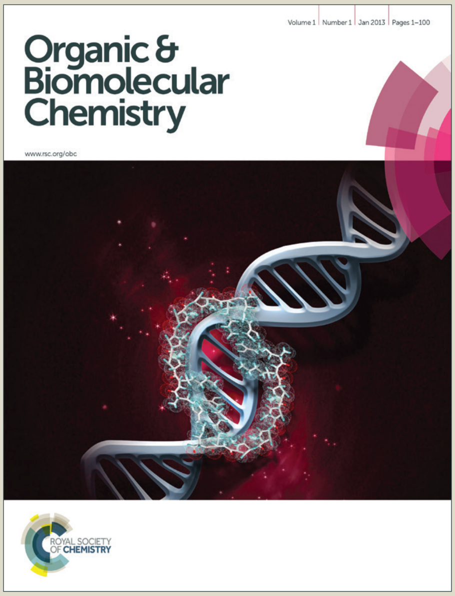

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ARTICLE TYPE

KI-catalyzed arylation of benzothiazoles from the coupling of aryl aldehydes with benzothiazoles in neat water

Yuyu Gao, Qiuling Song, Guolin Cheng, and Xiuling Cui*

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KI-catalyzed oxidative coupling of benzothiazoles with aryl aldehydes has been developed using TBHP as an oxidant in neat water under metal free conditions. Various 2-aryl benzothiazoles were prepared in 36-79% yields for 28 examples. The mechanistic studies suggested that this transformation proceeded via a radical process.

2-Aryl benzothiazoles are highly important scaffolds in the organic and medicinal chemistry due to their diverse biological and pharmacological properties, including antitumor, anti-convulsant, and anti-viral, which are exemplified in Figure 1.[1]

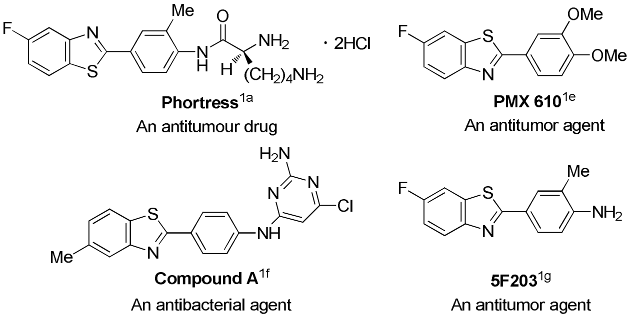
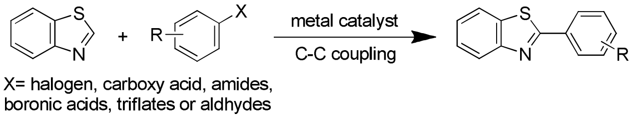
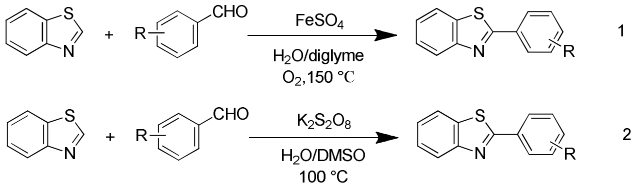


Figure 1 Examples of 2-ary benzothiazole with bioactivities.

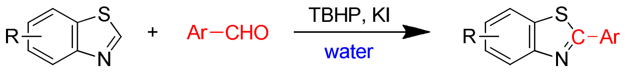
Conventional synthetic methods, including the metal-catalyzed intramolecular cyclization of thioformanilides[2] and the condensation of 2-aminothiophenol with carboxylic acids or aldehydes,[3] suffer from difficulties in the preparation of the starting materials due to their being easily oxidized. Alternatively, 2-aryl benzothiazoles have been successfully synthesized by transition metal-catalyzed cross-coupling of benzothiazoles with aryl halides,[4] arylsilanes,[5] aromatic carboxylic acids,[6] aryl boronic acids,[7] sodium sulfinates[8], and aryl triflates[9] (Scheme 1). Recently, Liu and co-workers reported an iron-catalyzed arylation of benzothiazoles with aryl aldehydes (Scheme 2, Eq. 1).[11] The metal catalyst or organometallic reagent would lead to potential metal contamination of the products that is particularly significant in the pharmaceutical industry. Yang and co-workers described their elegant work on the construction of 2-aryl benzothiazoles mediated by $K_2S_2O_8$ oxidative condensation of benzothiazoles with aryl aldehydes (Scheme 2, Eq. 2).[12] However, this transformation proceeded in organic solvents, and not applicable to electron-deficient aryl aldehydes. The development of mild and friendly environmental approach for the direct synthesis of 2-aryl benzothiazoles especially using cheap and commercially available aryl aldehydes as aryl source has attracted much interest. Herein, we report an arylation of benzothiazoles with aryl aldehydes catalyzed by KI in neat water under metal free conditions (Scheme 3).



Scheme 1 Metal catalyzed cross-coupling of benzothiazoles with pre-functionalized arene.



Scheme 2 Recent development of arylation of benzothiazoles with benzaldehydes.



Scheme 3 Arylation of benzothiazoles with aryl aldehydes in water.

The condensation of benzothiazole (**1a**) with benzaldehyde (**2a**) was initially chosen as a model reaction to screen the various reaction parameters. The arylation product was obtained in only 10% yield using TBHP (70% aq.) as an oxidant at 100 ℃ (Table 1, entry 1). Other peroxides, such as TBPB (*tert*-butyl peroxybenzoate), DTBP (di-*tert*-butyl peroxide), mCPBA (3-

Engineering Research Center of Molecular Medicine, Ministry of Education, Key Laboratory of Xiamen Marine and Gene Drugs, Institutes of Molecular Medicine and School of Biomedical Sciences, Huaqiao University, Xiamen, 361021
E-mail: cuixl@hqu.edu.cn

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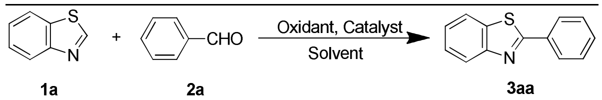
chloroperbenzoicacid), benzoyl peroxide (50% aq.) and TBHP in decane or in toluene, disfavoured this reaction (Table 1, entries 2-7). The yield could reach to 49% in the presence of 10 mol% KI (Table 1, entries 8) and was improved to 66% when 1 mL of water was added (Table 1, entry 9). 72% yield could be obtained by increasing the amount of KI to 20 mol% (Table 1, entry 10). Bu_4NI could also give the similar yield (Table 1, entry 11). Transition metal salt, such as $FeCl_2$•$4H_2O$ and $CuCl_2$•$2H_2O$, only gave the desired product in 40% and 30% yields respectively (Table 1, entries 12, 13). I_2 was also screened as a terminal oxidant. Only 43% isolated yield was obtained with the stoichiometric amount of I_2 (Table 1, entry 14). When the organic solvent was added, which made the reaction proceed in the homogenous solution, the yields decreased to 7% and 34% yields for MeCN and DMSO, respectively (Table 1, entries 15, 16). Moreover, the yields were reduced by decreasing the reaction temperature (Table 1, entries 17, 18). When the reaction was carried out in the air and oxygen atmosphere, the yield decreased to 50% and 41%, respectively, perhaps due to the oxidation of the aldehydes to the corresponding acids (Table 1, entries 19, 20).

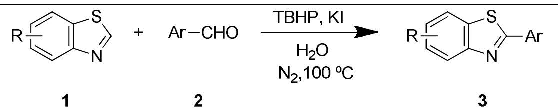
Table 1 Optimization of the reaction conditions for the condensation of benzothiazole (**1a**) with benzaldehyde (**2a**) [α]

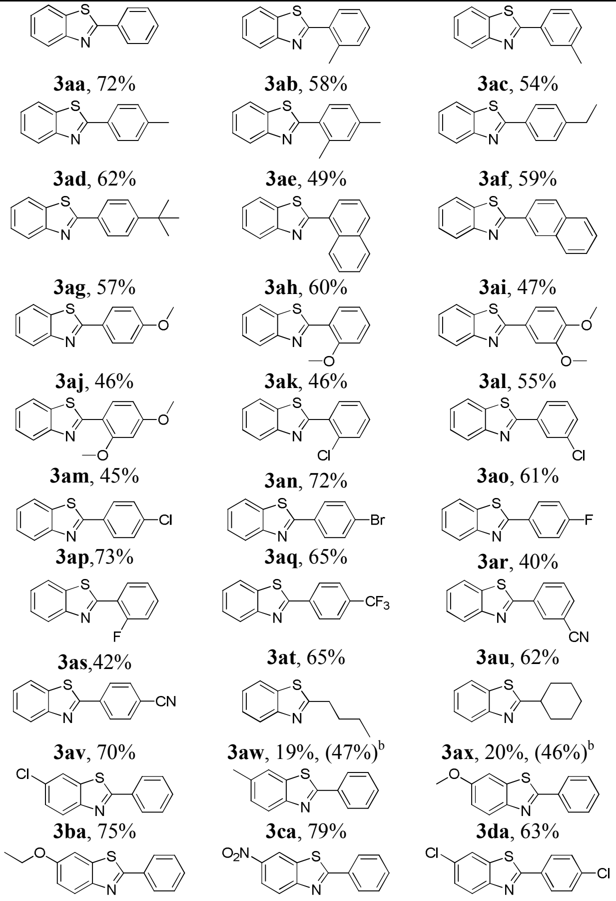


Entry	Oxidant	Catalyst (mol%)	Solvent	T (°C)	Yield(%)[b]
1	TBHP (70% aq.)	—	—	100	10
2	TBPB	—	—	100	nr
3	DTBP	—	—	100	nr
4	mCPBA	—	H_2O	100	8
5	Benzoyl peroxide (50% aq.)	—	—	100	9
6	TBHP (5.5 N in decane)	—	—	100	nr
7	TBHP (5 N in toluene)	—	—	100	nr
8	TBHP (70% aq.)	KI (10)	—	100	49[c]
9	TBHP (70% aq.)	KI (10)	H_2O	100	66[c]
10	**TBHP (70% aq.)**	**KI (20)**	**H_2O**	**100**	**72[c]**
11	TBHP (70% aq.)	Bu_4NI (20)	H_2O	100	72[c]
12	TBHP (70% aq.)	$FeCl_2$ • 4 H_2O (20)	H_2O	100	40[c]
13	TBHP (70% aq.)	$CuCl_2$ • 2 H_2O (20)	H_2O	100	30[c]
14	I_2 (1.2 eq.)	—	H_2O	100	43[c]
15	TBHP (70% aq.)	KI (20)	MeCN-H_2O (1:1)	100	7
16	TBHP (70% aq.)	KI (20)	DMSO-H_2O (1:1)	100	34
17	TBHP (70% aq.)	KI (20)	H_2O	60	20[c]
18	TBHP (70% aq.)	KI (20)	H_2O	80	59[c]
19	TBHP (70% aq.)	KI (20)	H_2O	100	50[c, d]
20	TBHP (70% aq.)	KI (20)	H_2O	100	41[c, e]

[a] Reaction conditions: **1a** (0.5 mmol), **2a** (0.75 mmol), oxidant 1.5 mmol, solvent (1 mL), N_2, 8 h; [b] GC yield based on **1a**; [c] Isolated yield based on **1a**; [d] air; [e] with oxygen balloon.

Table 2 Arylation of benzothiazoles with various aldehydes[a]





3aa, 72% **3ab**, 58% **3ac**, 54%

3ad, 62% **3ae**, 49% **3af**, 59%

3ag, 57% **3ah**, 60% **3ai**, 47%

3aj, 46% **3ak**, 46% **3al**, 55%

3am, 45% **3an**, 72% **3ao**, 61%

3ap,73% **3aq**, 65% **3ar**, 40%

3as,42% **3at**, 65% **3au**, 62%

3av, 70% **3aw**, 19%, (47%)[b] **3ax**, 20%, (46%)[b]

3ba, 75% **3ca**, 79% **3da**, 63%

3ea, 54% **3fa**, 36% **3bp**, 58%

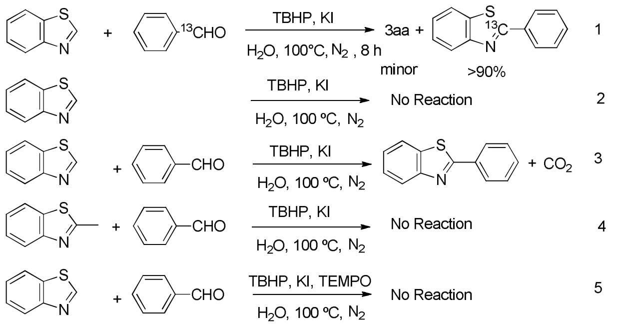
[a] Reaction conditions: **1** (0.5 mmol), **2** (0.75 mmol), TBHP (70% aqueous solution) (1.5 mmol), KI (0.1 mmol), H_2O (0.5 mL), 100 ºC, 8 h under N_2, isolated yield.

[b] Reaction conditions: after 4 h, the second part of **2** (0.75 mmol), TBHP (70% aqueous solution) (1.5 mmol) and KI (0.1 mmol) were added.

Under the optimal reaction conditions, the scope of substrates was investigated. The results were listed in Table 2. The reaction worked well for a wide variety of substituted benzaldehydes, affording the corresponding 2-aryl substituted benzothiazoles in ranging from 36% to 79% yields for 28 examples. There were no significant steric effects for benzaldehydes. *O*-, *m*-, *p*-methyl benzaldehydes gave the similar yields (**3ab**–**3ad**). Bulky group, such as *tert*-butyl (**3ag**), 1-naphenyl (**3ah**), 2-naphenyl (**3ai**), and di-methoxy (**3al**, **3am**), could give moderate yields. Electron-withdrawing groups such as trifluoromethyl (**3at**) and cyano (**3au**, **3av**) also afforded the corresponding 2-substituted benzothiazoles in moderate yields. The aliphatic aldehydes produced the desired products, but in low yields. However, the yields could be improved by doubling the quantities of aldehydes and TBHP (**3aw**, **3ax**). Benzothiazoles substituted by withdrawing and donating groups worked well under the optimized conditions (**3ba–3fa, 3bp**). Halogen group in either aldehyde or benzothiazole could be survived well under the standard reaction conditions and no cleavage of the C-halogen bond was observed

(**3an**–**3as**, **3ba**, **3bp**). While, benzimidazole and benzoxazole were decomposed under the standard conditions and no product was detected.

To clarify the reaction mechanism, some controlled experiments were carried out under the optimized conditions as follows, 1) ^{13}C-labled benzaldehyde was used as a substrate instead of benzaldehyde. A ^{13}C-labeled 2-phenyl benzothiazole was detected as a major product (>90%) by NMR (Scheme 5, Eq. 1), which indicated that this transformation did not take a decarbonylative or decarboxylate pathway, but might go through a ring-opening mechanism[14]. 2) Under the standard reaction conditions, benzothiazole would remain unchanged in the absence of aldehyde (Scheme 5, Eq. 2). Therefore, aldehydes were proposed to promote the ring-opening process. 3) Furthermore, CO_2 was generated and made the clear limewater become cloudy (Scheme 5, Eq. 3). 4）The condensation of 2-methylbenzothiazole with benzaldehyde (**2b**) could not give the desired product even prolonging the reaction time to 20 h (Scheme 5, Eq. 4). It was likely that the C2 of benzothiazole was oxidated into CO_2 and 2-methyl group hindered such oxidation. 5）When 2, 2, 6, 6-tetramethyl-1-piperidinyloxy (TEMPO) was added to this reaction system, the reaction was hampered (Scheme 5, Eq. 5). This result suggested that this transformation might go through a radical process.

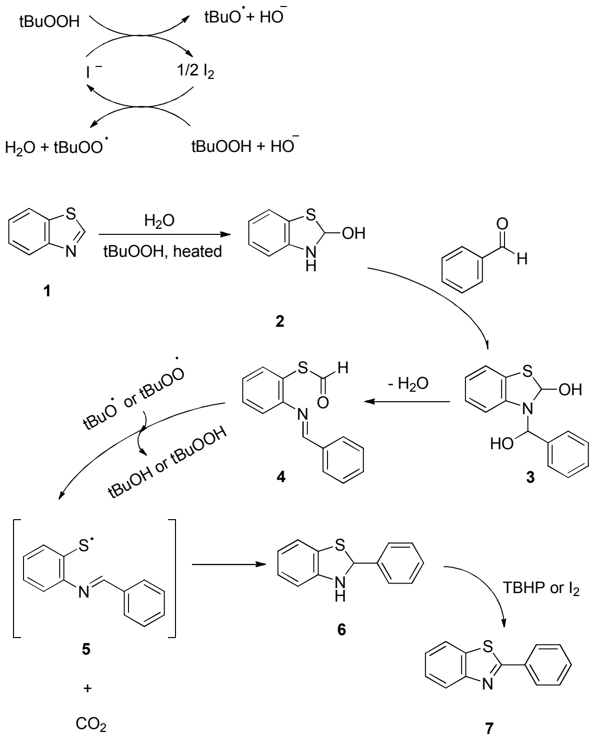


Scheme 5 Controlled experiments.

Based on the results obtained, an aldehyde assisted ring-opening mechanism was proposed as shown in Scheme 6. Firstly, benzothiazole **1** reacted with water to give 2-hydroxy-1,3-dihydrobenzothiazole **2**. The NH then reacted with benzaldehyde to give an aminal **3**. Loss of water then gave a Schiffs base **4**. At the same time, *tert*-butoxyl and *tert*-butylperoxyl radical were formed through the reaction of TBHP with I^- or I_2[16,17]. Subsequently, these radicals promoted **4** to convert into intermediate **5** via a thio-ene radical process[3e,15]. Intermediate **5** was highly reactive and would fast undergo an annulation process to afford **6**. Thereafter, **6** was oxidated by TBHP or I_2 and gave the desired product **7**.

Conclusion

A general and efficient procedure for the direct arylation of benzothiazoles with aryl aldehydes in neat water has been developed, affording the arylated products in 36%–79% yields for 28 examples. This transformation was proposed to go through a radical mechanism by using TBHP as a stoichiometric oxidant and KI as a catalyst.



Scheme 6 Proposed reaction mechanism.

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