## CuBr/H<sub>2</sub>O<sub>2</sub>-Mediated Oxidative Coupling of *N*,*N*-Dialkylarylamines in Water: A Practical Synthesis of Benzidine Derivatives

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**Abstract:**  $CuBr/H_2O_2$  was deployed into mediating the oxidative coupling reaction of *N*,*N*-dialkylarylamines in water, which gave benzidine derivatives in an economically and environmentally satisfying manner.

Key words: oxidative coupling, aqueous reaction, N,N-dialkylaryl-amine, CuBr,  $H_2O_2$ 

Benzidine derivatives have received growing interest for manufacturing materials due to a tunable electric conductivity, which admitted to diverse applications such as organic light-emitting diodes,<sup>1,2</sup> organic field-effect transistors,<sup>3</sup> organic solar cells,<sup>4</sup> and organic photoconductors.<sup>5</sup> A number of methods for the coupling reaction have been reported.<sup>6–11</sup> Among them, oxidative coupling of aniline derivatives provided an efficient access to benzidine derivatives. Recently, TiCl<sub>4</sub><sup>10</sup> and 1,8bis(diphenylmethylium)naphthalenediyl dications<sup>11</sup> were both reported to be effective oxidants for such coupling reactions, although the large excess of anilines (in the former) and the relatively hard-to-obtain dications (in the latter) retarded their acceptance as practical approaches. Very recently, our group reported a more practical and environmentally friendly method using cerium ammonium nitrate (CAN)<sup>12</sup> to mediate such reactions in water. However, this approach was not suitable for some solid-state substrates that were difficult to dissolve in water. On the consideration of current attention in the development of more efficient, environmentally friendly and general methods for chemical synthesis,<sup>13,14</sup> it could be highly desirable to develop a transition metal-mediated oxidative coupling reaction of tertiary aromatic amines in water. Herein we would like to report the coupling reaction of *N*,*N*-dialkylanilines in the presence of CuBr and  $H_2O_2$  in water gave corresponding N, N, N', N'- tetraalkylbenzidines (Scheme 1).





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Copper derivatives have been known to mediate the oxidative coupling of aryls to obtain biaryls.<sup>15–20</sup> In this broad context, copper(II) reagent was the mainly used oxidant for the coupling reaction of substrates with low oxidative potential, such as naphthols and naphthylamines.<sup>21–26</sup> Cu(I)-catalyzed aerobic oxidative coupling of 2-naphthol derivatives has also been reported.<sup>27</sup> However, in the case of oxidative coupling of aniline derivatives, all these copper reagents have never been involved, most probably due to their relatively lower oxidative activities. Seeking for a more active copper oxidant is challenge. We have found that anilines could be oxidized with CuBr in the presence of H<sub>2</sub>O<sub>2</sub> in water to give benzidine derivatives in high yields. Water as solvent clearly has both economical and environmental advantages.<sup>13,14</sup>

To begin our study, various copper salts such as  $CuCl_2$ ,  $Cu(OAc)_2$ ,  $CuCl/H_2O_2$ ,  $CuBr/H_2O_2$ ,  $CuI/H_2O_2$  and  $CuCl_2/H_2O_2$  were examined for the desired reaction (Table 1). All the Cu(II) salts were inefficient and  $CuBr/H_2O_2$  was proved to be the best one.  $CuCl/H_2O_2$  showed lower activity and  $CuI/H_2O_2$  appeared to be inert in this reaction.

 Table 1
 Various Copper Salts for the Coupling Reaction of 2a<sup>a</sup>

Entry	Salts (1 equiv)	H <sub>2</sub> O <sub>2</sub> (equiv)	Yield (%) <sup>b</sup>
1	CuCl <sub>2</sub>	_	0
2	Cu(OAc) <sub>2</sub>	_	0
3	CuCl	1	8
4	CuCl	5	23
5	CuCl	10	34
6	CuBr	5	58
7	CuBr	10	72
8	CuBr	20	55
9	CuI	5	Trace
10	CuI	10	Trace
11	CuCl <sub>2</sub>	10	0

 $^a$  Conditions: N,N-diethylaniline (1 mmol), H<sub>2</sub>O (3 mL), 30% H<sub>2</sub>O<sub>2</sub> was added at 0 °C in H<sub>2</sub>O and the reaction was kept at 0–25 °C for 10 h.

<sup>b</sup> Isolated yield.

To improve the yield,  $H_2O_2$  was added at 0 °C in water in order to minimize the possibility of decomposition of  $H_2O_2$ .<sup>28</sup> Various ratios of *N*,*N*-diethylaniline (**1a**) and CuBr as well as  $H_2O_2$  were checked and the best yield was obtained when the **1a**/CuBr/ $H_2O_2$  ratio was 1:1:10.<sup>29</sup> The yield decreased when the amount of CuBr or  $H_2O_2$  was reduced. However, when the amount of  $H_2O_2$  was increased to 20 equivalents, the yields of **2a** also decreased. It is important to note that the reaction did not proceed in the absence of either CuBr or  $H_2O_2$ .

Under the optimized conditions, various tertiary aromatic amines were transformed to corresponding benzidine derivatives. Representative results were listed in Table 2. Compared with the coupling reaction mediated by cerium ammonium nitrate,<sup>12</sup> the solubility of substrate was not a problem in the CuBr/H<sub>2</sub>O<sub>2</sub> system, even solid state 3,5dimethyl-*N*,*N*-diethylaniline (**1h**) also gave good yields of *N*,*N*,*N'*,*N'*-tetraethyl-3,3',5,5'-tetramethyl-benzidine (**2h**, entry 8). The reaction of aniline derivative with electronwithdrawing substituted group such as chloride on the phenyl ring did not proceed under the reaction conditions, which was suspected to be the result of low electron density of phenyl ring.

The coupling product 2a was also confirmed by X-ray crystal structure analysis as shown in Figure 1.<sup>33</sup> It was interesting to note that two configuration structures of 2a both existed in the crystal.

In connection with the mechanism of this reaction, two key points should be considered: (1)  $Cu(I)/H_2O_2$  was the active one instead of Cu(II) salts or  $Cu(II)/H_2O_2$ . In other words, the copper should be more active and highly valent species generated from Cu(I) and  $H_2O_2$ ; (2) coordination process of amine to copper species was suspected to be involved. Accordingly, one possible mechanism is proposed in Scheme 2. Firstly, Cu(I) salts were oxidized by  $H_2O_2$  to give more active Cu(III)=O precursor 3,<sup>34</sup> which coordinated with tertiary amine leading to complex 4. Due to the high electron-withdrawing ability of Cu(III) species, a one-electron transfer process occurred from the tertiary amine to the copper, which resulted in radical cation

Table 2 The Coupling Reaction of N,N-Dialkylarylamines in the CuBr/H<sub>2</sub>O<sub>2</sub> System<sup>a</sup>

Entry	Substrate	Product <sup>b</sup>	Yield (%) <sup>c</sup>
1	Et Et	Et N-N-Et	72
	1a	$2a^{10}$	
2	Me N Me	Me N Me	51
	1b	$2b^{10}$	
3	Ne Ní Et	Me Et' N- K Et	57
	1c	$2c^{10}$	
4	Me N Bu	Me N Bu	53
	1d	<b>2d</b> <sup>30</sup>	
5	, <sup>i-Pr</sup> Bu	<sup>i-Pr</sup> N- Bu	62
	1e	$2e^{31}$	
6	, Bu N. Bu	Bu N Bu	49
	1f	<b>2f</b> <sup>32</sup>	
7			76
	1g	$2g^{10}$	
8	Et N.	Et Et	74
	1h	$2h^{11}$	

<sup>a</sup> Conditions: *N*,*N*-dialkylarylamines (1 mmol), CuBr (1 mmol), H<sub>2</sub>O<sub>2</sub> (10 mmol), H<sub>2</sub>O

(3 mL), initiated at 0 °C and kept at 0–25 °C for 10 h.

<sup>b</sup> The spectra and physical data of known products have been reported in literature.

<sup>c</sup> Isolated yield.







Figure 1 Configuration of 2a in crystalline form

**5** and inert Cu(II) residue. The radical cation **5** dimerized to give diiminium ion **6**, which underwent deprotonation to afford product **2** after normal work-up.

In conclusion,  $CuBr/H_2O_2$ -mediated oxidative coupling reaction of *N*,*N*-dialkylarylamine in water opened a practical way for synthesis of benzidines. Compared with other methods for synthesizing benzidine derivatives, this approach was highly efficient and low cost. Moreover, the avoidance of organic solvent accorded with current attention of green chemistry. The scope, mechanism and synthetic applications of this reaction are currently under investigation.

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   (20) Description of the second secon
- (29) Representative Procedures. CuBr (144 mg, 1 mmol) and N,N-diethylaniline 1a (159 μL, 1 mmol) was added into H<sub>2</sub>O (3 mL) at 0 °C under N<sub>2</sub>. Then, H<sub>2</sub>O<sub>2</sub> (1 mL, 10 mmol, 30% aq solution) was added dropwise

within 1 min. The reaction mixture was kept at 0 °C for 2 h, then further stirred at 25 °C for 8 h. The reaction mixture was quenched by aq K<sub>2</sub>CO<sub>3</sub> solution and the organic residue was extracted with Et<sub>2</sub>O (2 × 2 mL). The combined extract was dried over anhyd MgSO<sub>4</sub>. The solvent was removed and the residue was chromatographed on an Al<sub>2</sub>O<sub>3</sub> column.

*N*,*N*,*N*',*N*'-tetraethylbenzidine(**2a**) was isolated using 1:50 EtOAc-petroleum ether mixture as eluent (108 mg, 72%). <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 7.40 (4 H, d, *J* = 8.6 Hz), 6.71 (4 H, d, *J* = 8.6 Hz), 3.35 (8 H, q, *J* = 7.2 Hz), 1.15 (12 H, t, *J* = 7.2 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 146.2, 128.8, 127.0, 112.1, 44.4, 12.6. ESI-MS: *m*/*z* = 297 [M + H<sup>+</sup>].

- (30) *N,N'*-Dimethyl-*N,N'*-dibutylbenzidine (2d): white solid, 53% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 7.42 (4 H, d, *J* = 8.9 Hz), 6.72 (4 H, d, *J* = 8.9 Hz), 3.30 (4 H, br), 2.93 (6 H, s), 1.52– 1.58 (4 H, m), 1.29–1.38 (4 H, m), 0.94 (6 H, t, *J* = 7.2 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 147.8, 129.1, 126.9, 112.4, 52.6, 38.4, 28.9, 20.4, 14.0. ESI-MS: m/z = 325 [M + H<sup>+</sup>].
- (31) *N,N'*-Diisopropyl-*N,N'*-dibutylbenzidine (2e): white solid, 62% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>):  $\delta$  = 7.40 (4 H, br), 6.75 (4 H, br), 4.07 (4 H, br), 3.13 (4 H, br), 1.53–1.61 (4 H, m), 1.18 (12 H, d, *J* = 6.5 Hz), 0.96 (6 H, t, *J* = 7.2Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>):  $\delta$  = 147.1, 129.1, 126.9, 113.3, 48.5, 43.8, 31.6, 20.4, 20.0, 14.0. ESI-MS: *m*/*z* = 381 [M + H<sup>+</sup>].
- (32) *N*,*N*,*N*',*N*'-Tetrabutylbenzidine (2f): white solid, 49% yield. <sup>1</sup>H NMR (CDCl<sub>3</sub>): δ = 7.40 (4 H, br), 6.69 (4 H, br), 3.28 (8 H, br), 1.54–1.62 (8 H, m), 1.30–1.41 (8 H, m), 0.96 (12 H, t, *J* = 7.2 Hz). <sup>13</sup>C NMR (CDCl<sub>3</sub>): δ = 146.5, 128.5, 126.9, 111.9, 50.8, 29.5, 20.4, 14.0. ESI-MS: *m*/*z* = 409 [M + H<sup>+</sup>].
- (33) Compound **2a**:  $C_{20}H_{28}N_2$ , crystallized in monoclinic, space group *C*2/c with cell parameters: a = 16.0904 (19), b = 15.7307 (19), c = 13.9754 (17)Å<sup>3</sup>, a = 90.00,  $\beta = 91.843$ (2),  $\gamma = 90.00^\circ$ , V = 3535.5 (7)Å<sup>3</sup>,  $D_c = 1.114$  g/cm<sup>3</sup>, Z = 8. CCDC 269443.
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