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Oxidative Coupling of *N*,*N*-Dialkylanilines Using Iodic Acid and Sodium Nitrite

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A new reagent system, a combination of iodic acid and sodium nitrite has been investigated for oxidative coupling of *N*,*N*-disubstituted anilines. A facile *para*-selective coupling occurs to give benzidines at room temperature in water as a solvent. A tentative mechanism is proposed with some supporting experiments.

Benzidine derivatives have widespread applications in the field of organic light-emitting diodes,[1] organic field-effect transistors,[2] organic solar cells,[3] organic photoconductors,[4] and as crosslinking agents used in polyurethane plastics.[5] Oxidative coupling of *N*,*N*-dialkylated anilines is an important approach in organic synthesis for construction of benzidine systems,[6] and a few methods are available, these includes oxidative systems naphthalen-1,8-diylbis(diphenylmethylium) dication,[7] Cu(II),[8] CuBr/H_2O_2,[9] $TiCl_4$,[10] and CAN.[11]

Our research group is actively engaged in exploring new utilities of hypervalent iodine compounds in organic synthesis,[12,13] and we would like to report successful use of iodic acid with sodium nitrite in water, which is considered to be a green solvent,[13] for oxidative coupling of *N*,*N*-dialkylanilines to give benzidines.

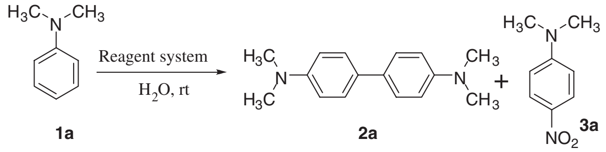
Use of HIO_3 in organic synthesis has several advantages like non toxicity, easy handling, and cost effectiveness. It is employed as an oxidant for many oxidative transformations such as oxidation of sulfides,[14] aromatic iodination,[15] nitrosation,[16] and deoximation.[17]

Initial experiments were performed with *N*,*N*-dimethylaniline (**1a**) as model substrate. When **1a** was treated with HIO_3 (2 equiv) and $NaNO_2$ (2 equiv) in water at room temperature *N*,*N*,*N*′,*N*′-tetramethylbenzidine (**2a**) was obtained in 70% yield along with 20% *N*,*N*-dimethyl-4-nitroaniline (**3a**) in just 5 min with complete consumption of starting material. To verify the role of HIO_3 and $NaNO_2$, reactions were carried out using different mole ratios of HIO_3/$NaNO_2$, monitoring the reaction by TLC, and results are summarized in Table 1.

When reaction was carried out with 1:2 equivalent of HIO_3 and $NaNO_2$ and vice versa poor yields of **2a** were shown (Entries 4 and 5). Further optimization revealed that the combination of substrate, HIO_3, and $NaNO_2$ in the ratio of 1:2:2 respectively in water at room temperature as the best reaction conditions for coupling. Use of other hypervalent iodine reagents like *o*-iodoxybenzoic acid (IBX) and HIO_4 were also viable, however, imparted **2a** in low yields. (Table 1, Entries 7 and 8).

When reaction of **1a** was carried with 1:1 equivalent of HIO_3 and $NaNO_2$ at 100 °C in water, **2a** and **3a** were formed in 30% and 25% yield, respectively, showing some additional spots on TLC indicative of by-product formation. Hence carrying out reaction at higher temperature is not significant.

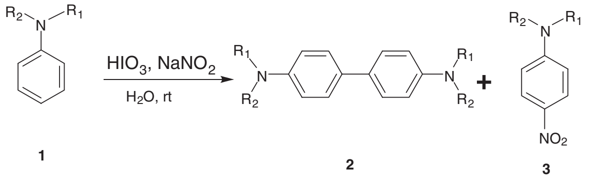
Table 1. Optimization of reaction conditions and screening of various hypervalent iodine reagents[a]



Entry	Reagent combination	Molar ratio	Reaction time[b]	Unreacted recovered[b]/%[c]	Yield/%[c]	
				1a	**2a**	**3a**
1	HIO_3/$NaNO_2$	2.0/2.0	5 min	—	70	20
2	HIO_3/$NaNO_2$	0.1/1.0	8 h	97	NR[e]	NR[e]
3	HIO_3/$NaNO_2$	1.0/0.1	8 h	90	4	—[d]
4	HIO_3/$NaNO_2$	1.0/1.0	8 h	75	14.5	—[d]
5	HIO_3/$NaNO_2$	1.0/2.0	8 h	75	17	—[d]
6	HIO_3/$NaNO_2$	2.0/1.0	8 h	70	22	3.5
7	IBX/$NaNO_2$	2.0/2.0	1 h	20	30	40
8	HIO_4/$NaNO_2$	2.0/2.0	30 min	20	60	10

[a]Reaction performed on 5 mmol scale using reagent combination at rt. [b]The reaction was incomplete even after stirring for 8 h in all cases where ratios of HIO_3 and $NaNO_2$ were less than 2:2 equivalent (Entries 2–6). [c]Isolated yields. [d] Trace amount. [e]NR: No reaction.

Table 2. Oxidative coupling reaction of *N*,*N*-dialkylanilines[18]



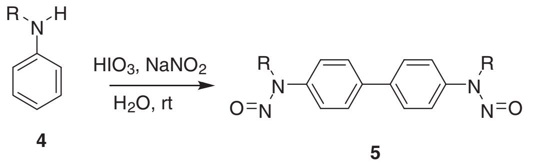
Entry	Substrate	R_1	R_2	Time /min	Products, Yield/%[a]	
1	**1a**	Me	Me	5	**2a**/70	**3a**/20
2	**1b**	Me	Et	5	**2b**/72	**3b**/20
3	**1c**	Me	Bu	10	**2c**/74	**3c**/15
4	**1d**	Me	CH_2Ph	10	**2d**/70	**3d**/20
5	**1e**	Et	Et	5	**2e**/71	**3e**/20
6	**1f**	Pr	Pr	15	**2f**/65	**3f**/25
7	**1g**	$(-CH_2-)_4$		25	**2g**/60	**3g**/30
8	**1h**	$(-CH_2-)_5$		30	**2h**/65	**3h**/30
9	**1i**	allyl	allyl	5	**2i**/70	**3i**/15
10	**1j**	allyl	Et	5	**2j**/62	**3j**/20
11	**1k**	$COCH_3$	Et	180	NR[b]	NR[b]

[a]Isolated yields. [b]NR: No reaction.

In order to check the generality and utility of the reaction, a variety of substrates were employed and results are summarized in Table 2. Inspection of the results reveals that oxidative coupling of various *N*,*N*-disubstituted anilines gave corresponding benzidines (Table 2, Entries 1–10) smoothly in good yields.

When the reaction was performed on *N*-benzyl-*N*-methylaniline, *N*,*N*-diallylaniline, and *N*-allyl-*N*-ethylaniline using the

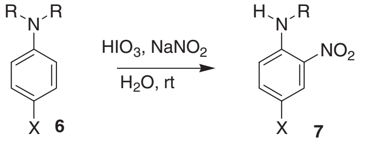
Table 3. Reaction of *N*-alkylanilnes[a]



Entry	Substrate	R	Time /min	Product Yield/%[b]
1	**4a**	Me	10	**5a**/92
2	**4b**	Et	10	**5b**/90

[a]Reaction performed on 5 mmol scale using reagent combination at rt.
[b]Isolated yields.

Table 4. Reaction of *para*-substituted *N*,*N*-dialkylanilines[a]



Entry	Substrate	R	X	Time /min	Product Yield/%[b]
1	**6a**	Me	Cl	5	**7a**/70
2	**6b**	Et	Cl	5	**7b**/72
3	**6c**	Pr	CH_3	10	**7c**/74
4	**6d**	Me	NO	120	NR[c]

[a]Reaction performed on 5 mmol scale using reagent combination at rt.
[b]Isolated yields. [c]NR: No reaction.

optimized reaction conditions, oxidative coupling occurred without effecting either benzylic or allylic positions or the double bond of the substrates. This observation highlights the chemoselectivity of the reaction (Table 2, Entries 4, 9, and 10). The coupling of *N*-ethyl-*N*-phenylacetamide did not occur and the starting material was recovered (Table 2, Entry 11).

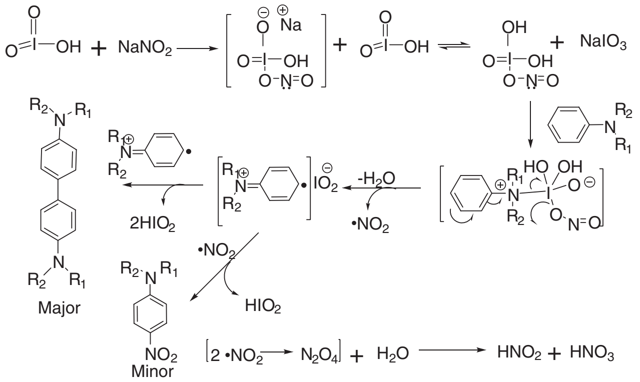
It was found that, in all cases (Table 2, Entries 1–10), only benzidines i.e., *para*-coupled products were selectively formed, and no *ortho*-, *ortho*–*para*-coupled products[9] were observed.

When *N*-monoalkylated anilines **4** were subjected to the optimized reaction conditions, *N*,*N*′-dialkyl-*N*,*N*′-dinitrosobenzidines **5** were obtained in high yields. The results are summarized in Table 3.

To get mechanistic insight some investigations were carried out. Reactions with *para*-substituted *N*,*N*-dialkylated anilines **6** did not provide coupled products, instead *ortho*-nitrated products **7** with *N*-monodealkylation were obtained in high yields (Table 4, Entries 1–3) and interestingly 4-nitroso-*N*,*N*-dimethylaniline remained unreacted (Table 4, Entry 4), this is valuable evidence to indicate that the 4-nitro products **3** are not formed via nitrosation followed by oxidation. Further substrate **1a** failed to react with HIO_3 and $NaNO_3$ under the reaction conditions to form *N*,*N*-dimethyl-4-nitroaniline (**3a**). This indicates that nitro products **3** are not arising out of simple nitration of **1**, through nitronium ion generated by oxidation of HNO_2.

With this preliminary evidence we propose a tentative mechanism as depicted in Scheme 1.

It can be concluded that iodic acid and sodium nitrite bring about a facile oxidative coupling of *N*,*N*-disubstituted anilines in water, a green solvent, to form selectively *para*-coupled products, benzidines.



Scheme 1. Proposed mechanism of reaction for benzidine formation.

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18 General procedure for oxidative coupling of *N*,*N*-dialkylarylamine: To a stirred solution of iodic acid (1.76 g, 10 mmol) and sodium nitrite (0.76 g, 10 mmol) in water (20 mL), substrate (5 mmol) was added immediately in one portion. Stirring continued until complete consumption of starting material as observed on TLC. After completion of reaction, the reaction mixture was diluted with water (20 mL) and a small amount of urea was added to destroy unreacted sodium nitrite and extracted with chloroform (2 × 15 mL). The organic layer was washed with saturated solution of sodium bicarbonate (2 × 30 mL) and brine solution (50 mL), dried over anhydrous sodium sulfate and concentrated under reduced pressure to give crude product. Pure product was obtained after column chromatography (silica gel, mesh size 60–120, eluent ethyl acetate:hexane 5:95). Spectral data of these compounds are available electronically as Supporting Information, http://www.csj.jp/journals/chem-lett/.