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# Concise Synthesis of Semicarbazides and Formylhydrazines *via* Direct Addition Reaction between Aromatic Azoarenes and *N*-Substituted Formamides

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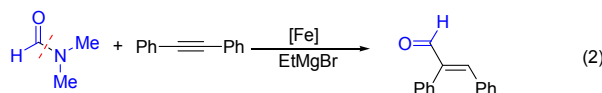
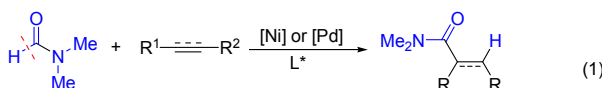
The addition reactions between aromatic azoarenes and *N*-substituted formamides are described. This direct and practical method provides a novel approach for the synthesis of formylhydrazines and semicarbazides in the presence of NaI/DTBP and imidazole/DCP catalytic systems, respectively. It can be seen that C–H or C–N from *N*-substituted formamides could be cleaved selectively under such transition-metal-free conditions. This is the first successful example of direct addition of *N*-substituted formamides to N=N bond.

In the past several years, *N,N*-Dimethylformamide (DMF) was not only used as the polar solvents for various catalytic reactions, but also employed as the multipurpose precursor for various units in various reactions.<sup>1</sup> Among these, formylation and aminocarbonylation are the most important contributions from DMF.<sup>2</sup> In this way, many groups focused on such transformations through direct substitution with carbon-halogen or C–H bond.<sup>3</sup> However, the intermolecular addition of formamides was attracted little attention. Until to 2009, Nakao and Hiyama firstly reported that the intermolecular hydrocarbonylation reactions of alkynes and 1, 3-dienes could be catalyzed by nickel and Lewis acid to synthesize unsaturated amides.<sup>4</sup> In 2010, Tsuji and co-workers demonstrated that formamides could be successfully added to internal or terminal alkynes to afford the same products.<sup>5</sup> It can be seen that this transformation undergoes the cleavage of C–H close to carbonyl group from formamides [Scheme 1, Eq. (1)]. Differently, Nakamura and co-workers<sup>6</sup> just found that the addition of DMF with alkenylmagnesium generated *in situ* from FeCl<sub>2</sub> and EtMgBr to produce an (*E*)- $\beta$ -unsaturated aldehyde through the cleavage of C–N close to carbonyl group from DMF [Scheme 1, Eq. (2)]. Therefore, the direct addition of DMF to carbon-carbon double bond and triple bond could provide an effective approach to prepare a series of unsaturated carbonyl compounds. Herein, we report the first transition-metal-free addition of formamides to nitrogen-nitrogen double bond *via* selective cleavage of C–H or C–N bond from formamides.

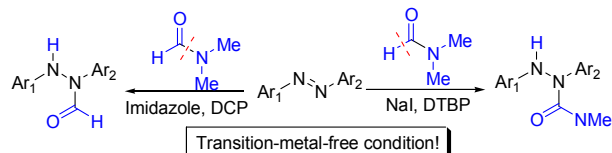
As we know that azo compounds, functioned as organic dyes, pigments, food additives, indicators and radical reaction initiators, are widely used in industry.<sup>7</sup> In recent years, studies on the chemistry of azodicarboxylates have received significant attention in organic synthesis.<sup>8</sup> Dialkyl azodicarboxylates are excellent

electrophiles, which have been successfully used for C–N bond formation reactions *via* the addition of C–H bond to the N=N double bond of dialkyl azodicarboxylates.<sup>9</sup> However, compared to dialkyl azodicarboxylates, the N=N double bond in aromatic azoarenes has less reactivity. To the best of our knowledge, only a very few of precedents have been reported for C–H addition to the N=N double bond of aromatic azoarenes.<sup>10</sup> For example, Kisch group disclosed one example of semiconductor-catalyzed photoaddition of olefins and enol ethers to 1,2-diazenes.<sup>10b</sup> However, in this paper, we will differently show a simple protocol for the preparation of the desired formylhydrazines and semicarbazides through the direct addition of formamides to aromatic azoarenes in the presence of NaI/ di-*tert*-butyl peroxide (DTBP) and imidazole/ dicumyl peroxide (DCP) catalytic systems, respectively.

Previous work:



Present work:



**Scheme 1.** Intermolecular addition of formamides to unsaturated bonds (C=C, C≡C and N=N)

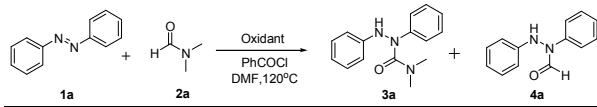
At the beginning of our investigation, readily available azobenzene (**1a**) and DMF (**2a**) were selected as the model substrates to optimize the reaction conditions, and the related results are listed in Table 1. It was found that the combination of azobenzene (**1a**, 0.5 mmol) with DTBP (2.0 mmol) in DMF at 120 °C for 24 h could generate the product **3a** in 25% yield (Table 1, entry 1). When PhCOCl (0.2 eq) was added to the reaction, we not only obtained **3a** in 31% yield, but also got the *N*-formylated product **4a** in 17% yield (Table 1, entry 2). To our delight, when the oxidant was replaced by DCP, the desired **4a** was obtained in 60% yield, while **3a** was not acquired (Table 1, entry 3). However, low yields were obtained when *t*-butyl hydroperoxide (TBHP) and *p*-benzoquinone (BQ) were used as oxidants (Table 1, entries 4-5). When the iodides were added to the catalyst system, the product was obviously improved to around 50%. Besides, the product **4a** was obtained in trace (Table 1, entries 6-9). Through the above examination of the data, we can conclude that when DTBP was used as oxidant, **3a** was obtained as the predominant product and when

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85 DCP was used as oxidant, **4a** was acquired as the main product. Without PhCOCl, the desired product **3a** was only obtained in 38% yield, and increased the amount of PhCOCl to 40 mol%, resulted in 65% yield of **3a** (Table 1, entry 11). However, changing the amount of NaI could not improve the product of **3a** (Table 1, entry 12). In traditional reports for the *N*-formylation of primary amines in DMF, imidazoles were often utilized.<sup>11</sup> Then, imidazole was added to the reaction when DCP was used as oxidant, and the product **4a** was obtained in 68% yield (Table 1, entry 13). However, the substituted imidazoles, some other heterocycles or changing the amount of PhCOCl were not favorable for the reaction (Table 1, entries 14-19).

**Table 1.** Optimization of reaction conditions for the reaction of azobenzene with DMF<sup>a</sup>



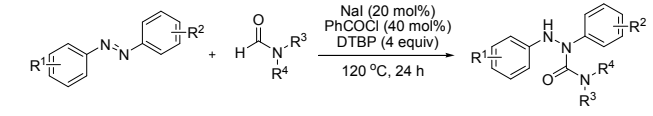
Entry	Oxidant	Additive (equiv)	Yield of <b>3a</b> (%) <sup>b</sup>	Yield of <b>4a</b> (%) <sup>b</sup>
1 <sup>c</sup>	DTBP	–	25	NR
2	DTBP	–	31	17
3	DCP	–	trace	60
4	TBHP	–	10	14
5	BQ	–	trace	trace
6	DTBP	I <sub>2</sub> (0.2)	47	trace
7	DTBP	NaI (0.2)	57	trace
8	DTBP	KI (0.2)	51	trace
9	DTBP	TBAI (0.2)	51	trace
10 <sup>c</sup>	DTBP	NaI (0.2)	38	trace
<b>11<sup>d</sup></b>	<b>DTBP</b>	<b>NaI (0.2)</b>	<b>65</b>	<b>trace</b>
12 <sup>c</sup>	DTBP	NaI (0.2)	42	trace
<b>13</b>	<b>DCP</b>	<b>imidazole (1.0)</b>	<b>10</b>	<b>68</b>
14	DCP	2-methylimidazole (1.0)	<10	55
15	DCP	4-methylimidazole (1.0)	<10	43
16	DCP	dipyridyl(1.0)	<10	15
17	DCP	piperazine(1.0)	<10	18
18 <sup>d</sup>	DCP	imidazole (1.0)	15	30
19 <sup>c</sup>	DCP	imidazole (1.0)	14	44

<sup>a</sup> Reaction conditions: azobenzene (0.5 mmol), oxidant (2 mmol, 4 eq), PhCOCl (20 mol%), DMF (2 mL), 120 °C, 24 h, air; <sup>b</sup> Yield of isolated product; <sup>c</sup> No PhCOCl; <sup>d</sup> PhCOCl (40 mol%); <sup>e</sup> PhCOCl (10 mol%).

With the optimized conditions of the aminocarbonylation of azobenzene in hand (Table 1, entry 11), we began to examine the scope and the limitation of this method (Table 2). As can be seen from Table 2, the reaction of different azoarenes with various formamides could generate the desired products in moderate to good yields. The *para*-substituted symmetrical azobenzenes with electron-withdrawing groups, such as F, Cl, Br, CF<sub>3</sub>O and CO<sub>2</sub>Et could react with DMF to afford the corresponding products **3b**, **3c**, **3d**, **3e** and **3i** in 35-63% yields. Besides, when the *para*-substituted unsymmetrical azobenzene 2-(4-bromophenyl)-1-(4-iodophenyl)-*N,N*-dimethylhydrazinecarboxamide was used to react with DMF, **3f** was obtained in 43% yield. Substitutions on the *meta*-positions were also well tolerated. 3,3-Dichloroazobenzene and 3,3-dibromoazobenzene coupled with DMF smoothly to afford the product **3g** and **3h** in 63% and 64% yields, respectively. Similarly,

as for unsymmetrical azobenzenes, reaction with formamides afforded the corresponding product **3j**, **3k** and **3l** with good yields. It is noteworthy that halo-substituted azobenzene compounds could also be tolerated well, which could be used for the further transformations. The reactions of other formamide derivatives with **1a** also gave the corresponding products (**3m-3p**) in moderate to excellent yields. Besides, the addition of *N*-benzylideneaniline with DMF afforded the corresponding products with reduced yields (**3q**).

**Table 2.** Preparation of semicarbazides through the addition reaction between aromatic azoarenes and *N*-substituted formamides<sup>a</sup>



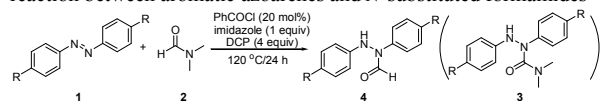
1	2	3
<b>3a</b> , 65%	<b>3b</b> , 35%	<b>3c</b> , 62%
<b>3d</b> , 63%	<b>3e</b> , 43%	<b>3f</b> , 43%(1.3:1) <sup>d</sup>
<b>3g</b> , 63%	<b>3h</b> , 64%	<b>3i</b> , 42%
<b>3j</b> , 53%(3:1) <sup>d</sup>	<b>3k</b> , 48%(1.5:1) <sup>d</sup>	<b>3l</b> , 50%(1.5:1) <sup>d</sup>
<b>3m</b> , 81% <sup>c</sup>	<b>3n</b> , 48%	<b>3o</b> , 37%
<b>3p</b> , 39%	<b>3q</b> , 20%	

<sup>a</sup> Reaction conditions: azobenzene (0.5 mmol), NaI (20 mol%), DTBP (2 mmol, 4 equiv), PhCOCl (40 mol%), DMF (2 mL), 120 °C, 24 h, air. <sup>b</sup> Yield of isolated product; <sup>c</sup> DCP as oxidant; <sup>d</sup> Ratio of regioisomers (Based on <sup>1</sup>HNMR)

Moreover, we examined the formylation of various azobenzenes as shown in Table 3. It was found that the reactions were carried out with moderate to good yields as for both electron-donating and electron-withdrawing groups on the aromatic rings from azobenzenes. As shown in entry 1, Table 1, the addition of azobenzene with DMF afforded **4a** in 68% yield and the X-ray crystallization could prove the structure (Table 3, entry 1). As expected, formylation of (*E*)-1,2-bis(4-fluorophenyl)diazene with DMF provided **4b** in 40% yield (Table 3, entry 2), while the (*E*)-1,2-bis(4-chlorophenyl)diazene and (*E*)-1,2-bis(4-bromophenyl)diazene gave the corresponding product **4c**, **4d** in 53% and 67% yields, respectively (Table 3, entries 3-4). It is probably due to the different electronic absorption of halogen. However, (*E*)-1, 2-bis(4-(trifluoromethoxy) phenyl)diazene only gave 30% yield. Besides,

the azobenzenes containing electron-donating groups, such as Me, gave the formylated products in 41% yields. To our disappointment, *N,N*-dimethylacetamide did not work (Table 3, entry 7).

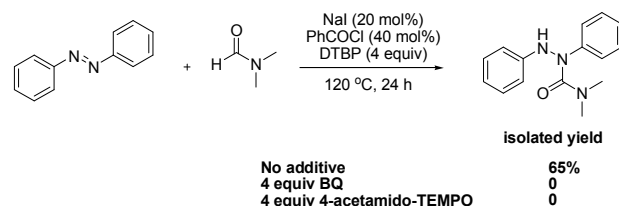
**Table 3.** Preparation of formylhydrazines through the addition reaction between aromatic azoarenes and *N*-substituted formamides<sup>a</sup>



Entry	Product 4	Yield of 4(%) <sup>b</sup>
1		68
2		40
3		53
4		67
5		30
6		41
7		NR

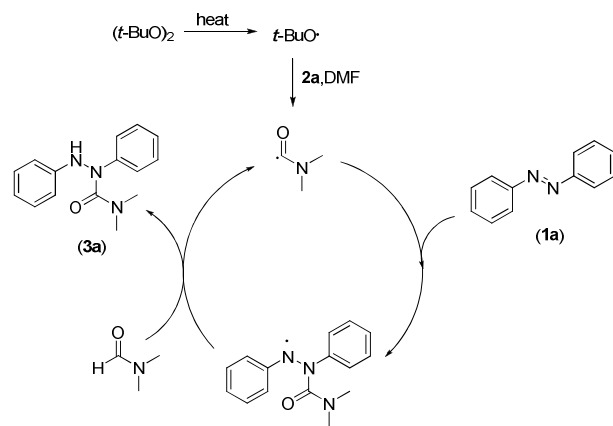
<sup>a</sup> Reaction conditions: azobenzene (0.5 mmol), imidazole (0.5 mmol, 1 equiv), DCP (2 mmol, 4 equiv), PhCOCl (20 mol%), DMF (2 mL), 120 °C, 24 h; <sup>b</sup> Yield of isolated product; <sup>c</sup> *N,N*-dimethylacetamide as **2a**.

To probe the mechanism of this transformation, some additional experiments in the presence of radical scavengers have been performed. As shown in Scheme 2, BQ and 4-acetamido-TEMPO (4 equiv) could completely inhibit the hydroacylation of formamides to azobenzenes in the presence of NaI/DTBP, which suggested that the transformation may proceed *via* a radical process. However, the formylation of azobenzene could not be inhibited using the catalytic system of imidazole/DCP when the radical scavengers 4-acetamido-TEMPO (4 equiv) was added, and the desired product was obtained in 50% yield.



**Scheme 2.** The control experiments to prove the mechanism

Based on the above reaction results, we have proposed the possible mechanism of the reaction as shown in Scheme 3. For the reaction between azobenzene and DMF in the presence of NaI/DTBP/PhCOCl, homolytic cleavage of DTBP will generate an alkoxy radical. Then, this radical species will abstract a hydrogen atom from DMF, thus leading to the desired free-radical of amide,<sup>3</sup> which undergoes the addition to **1a** to generate an adduct free-radical.<sup>8d,12</sup> Finally, this free-radical abstracts a hydrogen atom from DMF (generated during the reaction) to afford the desired **3a**. The role of NaI and PhCOCl is still not very clear and need to be investigated. In view of preparing formylhydrazines through the addition reaction between aromatic azoarenes and DMF, we assumed that DMF in the presence of PhCOCl, will generate the Vilsmeier reagents, which are usually prepared from *N,N*-disubstituted formamides and acid chlorides, and then the Vilsmeier reagents<sup>13</sup> reacted with azobenzene to give the hydroacylated product (**3**) and formylated product (**4**), and the mechanism is still under investigation.



**Scheme 3.** Plausible Mechanism

In summary, we have shown that the direct C–H addition of formamides to the *N=N* double bond of aromatic azo compounds under transition-metal-free catalytic conditions. It is interesting to find that such selective cleavage of the *N*-substituted formamides will afford the *N*-formylated products and hydroacylated products, which will be the direct and practical method to prepare formylhydrazines and semicarbazides in the presence of NaI/DTBP and imidazole/DCP catalytic systems, respectively. To date and to the best of our knowledge, this is the first report of direct hydroacylation and formylation of formamides to aromatic azo compounds. The further application of our method in biologically active molecules is underway in our laboratory.

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