RSC Advances

COMMUNICATION

View Article Online
View Journal | View Issue



Cite this: *RSC Adv.*, 2015, **5**, 19301

Received 25th December 2014
Accepted 2nd February 2015

DOI: 10.1039/c4ra17015f

www.rsc.org/advances



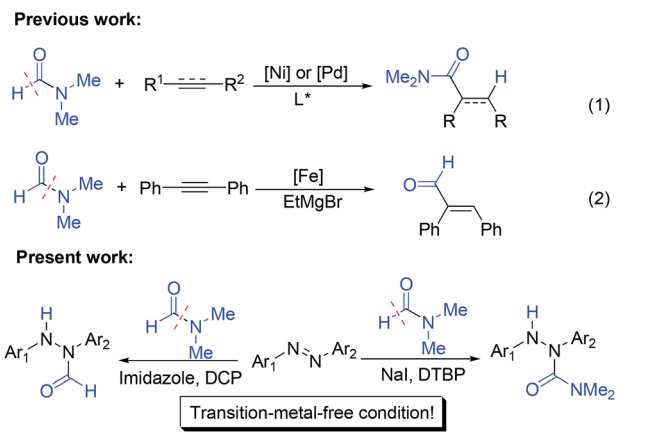
# Concise synthesis of semicarbazides and formylhydrazines *via* direct addition reaction between aromatic azoarenes and *N*-substituted formamides†

Defu Liu,[a] Jincheng Mao,*[ab] Guangwei Rong,[a] Hong Yan,[a] Yang Zheng[a] and Jie Chen[a]

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 a N=N bond.

In the past several years, *N*,*N*-dimethylformamide (DMF) was not only used as a polar solvent for various catalytic reactions, but also employed as a multipurpose precursor for various units in various reactions.[1] Among these, formylation and aminocarbonylation are the most important contributions from DMF.[2] In this way, many groups focused on such transformations through direct substitution with a carbon–halogen or C–H bond.[3] However, the intermolecular addition of formamides has attracted little attention. In 2009, Nakao and Hiyama first reported that the intermolecular hydrocarbamoylation reactions of alkynes and 1,3-dienes could be catalyzed by nickel and a Lewis acid to synthesize unsaturated amides.[4] In 2010, Tsuji and co-workers demonstrated that formamides could be successfully added to internal or terminal alkynes to afford the same products.[5] It can be seen that this transformation undergoes the cleavage of C–H close to carbonyl group of the formamides [Scheme 1, eqn (1)]. Differently, Nakamura and co-workers[6] found that the addition of DMF with alkenylmagnesium generated *in situ* from $FeCl_2$ and EtMgBr produced an (*E*)-β-unsaturated aldehyde through the cleavage of C–N close to carbonyl group of DMF [Scheme 1, eqn (2)]. Therefore, the direct addition of DMF to carbon–carbon double and triple bonds 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 a nitrogen–nitrogen double bond *via* selective cleavage of a C–H or C–N bond of a formamide.

As we know, azo compounds, that function as organic dyes, pigments, food additives, indicators and radical reaction initiators, are widely used in industry.[7] In recent years, studies on the chemistry of azodicarboxylates have received significant attention in organic synthesis.[8] 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.[9] 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




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

[a]*Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, P. R. China. E-mail: jcmao@suda.edu.cn*

[b]*State Key Laboratory of Oil and Gas Reservoir Geology and Exploitation, Southwest Petroleum University, Chengdu 610500, P. R. China*

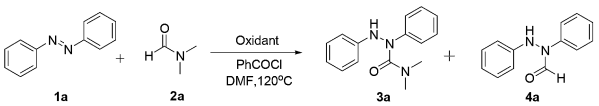
† Electronic supplementary information (ESI) available: Experimental procedures, $^1H$, $^{13}C$, HRMS spectral data and analytical data for the products. CCDC 1040947. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c4ra17015f

azoarenes.[10] For example, Kisch group disclosed one example of semiconductor-catalyzed photoaddition of olefins and enol ethers to 1,2-diazenes.[10b] However, in this paper, we will differently show an 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.

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 equiv.) 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 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 mmol%, 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.[11] 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).

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, $CF_3O$ and $CO_2Et$ 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

Table 1 Optimization of reaction conditions for the reaction of azobenzene with DMF[a]

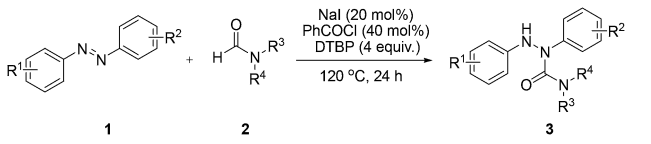



| Entry | Oxidant | Additive (equiv.) | Yield[b] of **3a** (%) | Yield[b] of **4a** (%) |
|---|---|---|---|---|
| 1[c] | DTBP | — | 25 | NR |
| 2 | DTBP | — | 31 | 17 |
| 3 | DCP | — | Trace | 60 |
| 4 | TBHP | — | 10 | 14 |
| 5 | BQ | — | Trace | Trace |
| 6 | DTBP | $I_2$ (0.2) | 47 | Trace |
| 7 | DTBP | NaI (02) | 57 | Trace |
| 8 | DTBP | KI (0.2) | 51 | Trace |
| 9 | DTBP | TBAI (0.2) | 51 | Trace |
| 10[c] | DTBP | NaI (0.2) | 38 | Trace |
| **11**[d] | **DTBP** | **NaI (0.2)** | **65** | **Trace** |
| 12[e] | DTBP | NaI (0.2) | 42 | Trace |
| **13** | **DCP** | **Imidazole (1.0)** | **10** | **68** |
| 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[d] | DCP | Imidazole (1.0) | 15 | 30 |
| 19[e] | DCP | Imidazole (1.0) | 14 | 44 |

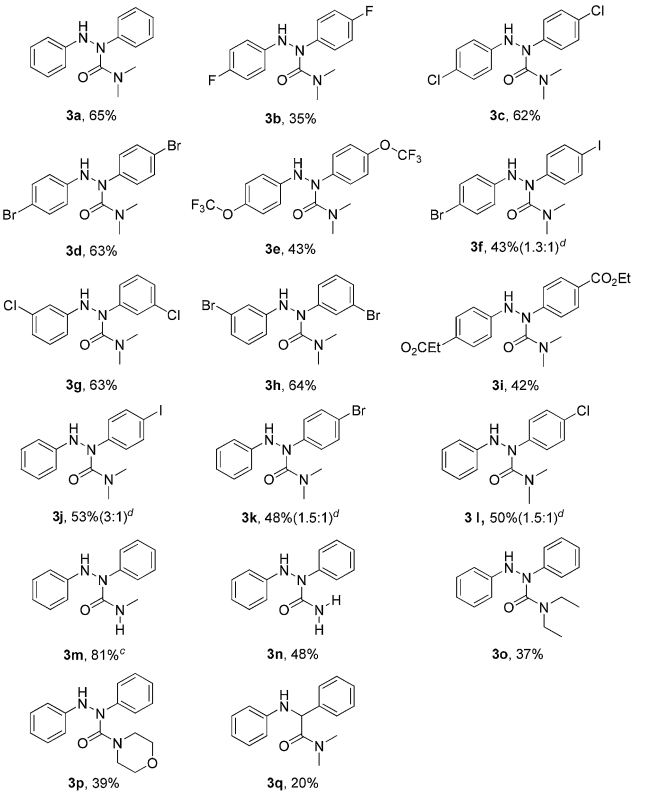
[a] Reaction conditions: azobenzene (0.5 mmol), oxidant (2 mmol, 4 equiv.), PhCOCl (20 mol%), DMF (2 mL), 120 °C, 24 h, air. [b] Yield of isolated product. [c] No PhCOCl. [d] PhCOCl (40 mol%). [e] PhCOCl (10 mol%).

Table 2 Preparation of semicarbazides through the addition reaction between aromatic azoarenes and *N*-substituted formamides[a,b]

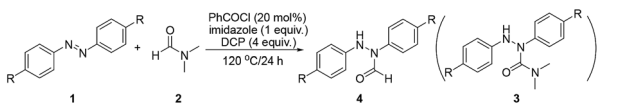



1 2 3

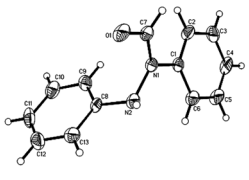
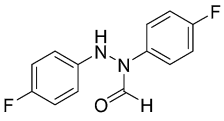
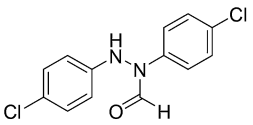
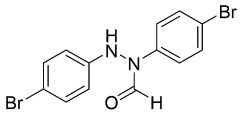
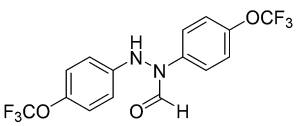
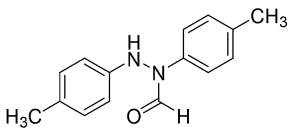
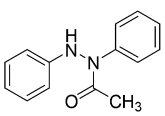



[a] Reaction conditions: azobenzene (0.5 mmol), NaI (20 mol%), DTBP (2 mmol, 4 equiv.), PhCOCl (40 mol%), DMF (2 mL), 120 °C, 24 h, air. [b] Yield of isolated product. [c] DCP as oxidant. [d] Ratio of regioisomers (Based on $^1$HNMR).

Table 3 Preparation of formylhydrazines through the addition reaction between aromatic azoarenes and *N*-substituted formamides[a]



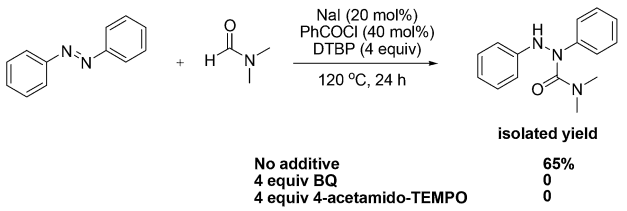

1 2 4 3

| Entry | Product 4 | Yield[b] of 4 (%) |
|---|---|---|
| 1 |  (4a) | 68 |
| 2 |  (4b) | 40 |
| 3 |  (4c) | 53 |
| 4 |  (4d) | 67 |
| 5 |  (4e) | 30 |
| 6 |  (4f) | 41 |
| 7[c] |  (4g) | NR |

[a] 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. [b] Yield of isolated product. [c] *N*,*N*-Dimethylacetamide as **2a**.

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**).

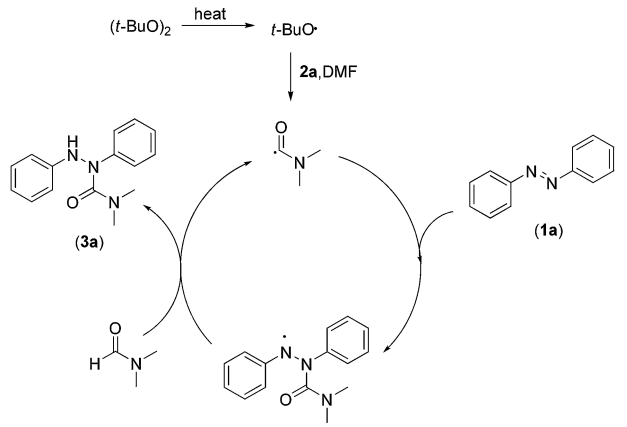
Moreover, we examined the formylation of various azobenzenes as shown in Table 3. It was found that the reactions were carried out with moderate to good yields as for both electron-donating and electron-withdrawing groups on the aromatic rings from azobenzenes. As shown in entry 1, Table 1, the addition 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).




Scheme 2 The control experiments to prove the mechanism.

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 inhabited 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.

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 alkoxyl radical. Then, this radical species will abstract a hydrogen atom from DMF, thus leading to the desired free-radical of amide,[3] which undergoes the addition to **1a** to generate an adduct free-radical.[8d,12] 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[13] 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.

## Acknowledgements

We are grateful to the grants from the Scientific Research Foundation for the Returned Overseas Chinese Scholars, State Education Ministry, the Priority Academic Program Development of Jiangsu Higher Education Institutions, and the Key Laboratory of Organic Synthesis of Jiangsu Province.

## Notes and references

1 (*a*) A. Jutand, *Chem. Rev.*, 2008, **108**, 2300; (*b*) M. C. Das, H. Xu, Z. Wang, G. Srinivas, W. Zhou, Y.-F. Yue, V. N. Nesterov, G. Qian and B. Chen, *Chem. Commun.*, 2011, **47**, 11715; (*c*) P. Supsana, T. Liaskopoulos, P. G. Tsoungas and G. Varvounis, *Synlett*, 2007, 2671; (*d*) Y. Liu, G. He, K. Chen, Y. Jin, Y. Li and H. Zhu, *Eur. J. Org. Chem.*, 2011, **76**, 5323; (*e*) J. Muzart, *Tetrahedron*, 2009, **65**, 8313; (*f*) S.-T. Ding and N. Jiao, *Angew. Chem., Int. Ed.*, 2012, **51**, 9226.

2 (*a*) G. Jones and S. P. Stanforth, *Org. React.*, 1997, **49**, 1; (*b*) M. Suchý, A. A. H. Elmehriki and R. H. E. Hudson, *Org. Lett.*, 2011, **13**, 3952; (*c*) K. Hosoi, K. Nozaki and T. Hiyama, *Org. Lett.*, 2002, **4**, 2849.

3 (*a*) J. Ju, M. Jeong, J. Moon, H. M. Jung and S. Lee, *Org. Lett.*, 2007, **9**, 4615; (*b*) T. He, H. Li, P. Li and L. Wang, *Chem. Commun.*, 2011, **47**, 8946.

4 Y. Nakao, H. Idei, K. S. Kanyiva and T. Hiyama, *J. Am. Chem. Soc.*, 2009, **131**, 5070.

5 T. Fujihara, Y. Katafuchi, T. Iwai, J. Terao and Y. Tsuji, *J. Am. Chem. Soc.*, 2010, **132**, 2094.

6 L. Ilies, T. Yoshida and E. Nakamura, *J. Am. Chem. Soc.*, 2012, **134**, 16951.

7 (*a*) R. G. Anderson and G. Nickless, *Analyst*, 1967, **92**, 207; (*b*) R. D. Athey Jr, *Eur. Coat. J.*, 1998, **3**, 146; (*c*) J. R. S. Hoult, *Drugs*, 1986, **32**, 18; (*d*) W. J. Sandborn, *Am. J. Gastroenterol.*, 2002, **97**, 2939.

8 (*a*) V. Nair, A. T. Biju, K. Mohanan and E. Suresh, *Org. Lett.*, 2006, **8**, 2213; (*b*) X. Liu, H. Li and L. Deng, *Org. Lett.*, 2005, **7**, 167; (*c*) A. Denis and C. Renou, *Tetrahedron Lett.*, 2002, **43**, 4171; (*d*) L. Ryu, A. Tani, T. Fukuyama, D. Ravelli, S. Montanaro and M. Fagnoni, *Org. Lett.*, 2013, **15**, 2554.

9 Y.-C. Qin, Q. Peng, J.-S. Song and D. Zhou, *Tetrahedron Lett.*, 2011, **52**, 5880.

10 (*a*) J. K. S. Wan and L. D. Hess, *J. Am. Chem. Soc.*, 1964, **86**, 2069; (*b*) R. Künneth, C. Feldmer, F. Knoch and H. Kisch, *Chem.–Eur. J.*, 1995, **7**, 441; (*c*) Y. Kgeyama and S. Murata, *J. Org. Chem.*, 2005, **70**, 3140.

11 (*a*) T. Kitagawa, J. Arita and A. Nagahata, *Chem. Pharm. Bull.*, 1994, **42**, 1655; (*b*) T. Kitagawa, J. Ito and C. Tsutsui, *Chem. Pharm. Bull.*, 1994, **42**, 1931.

12 Y.-C. Qin, Q. Peng, J.-S. Song and D. Zhou, *Tetrahedron Lett.*, 2011, **52**, 5880.

13 (*a*) A. Vilsmeier and A. Haack, *Ber. Dtsch. Chem. Ges.*, 1927, **60**, 119; (*b*) Z. Arnold and J. Zemlicka, *Proc. Chem. Soc., London*, 1958, 227; (*c*) Z. Arnold and A. Holy, *Collect. Czech. Chem. Commun.*, 1961, **26**, 3059; (*d*) G. Jones and S. P. Stanforth, *Org. React.*, 2000, **56**, 355; (*e*) S. Brahma and J. K. Ray, *Tetrahedron*, 2008, **64**, 2883; (*f*) A. Chan and K. A. Scheidt, *J. Am. Chem. Soc.*, 2008, **130**, 2740.