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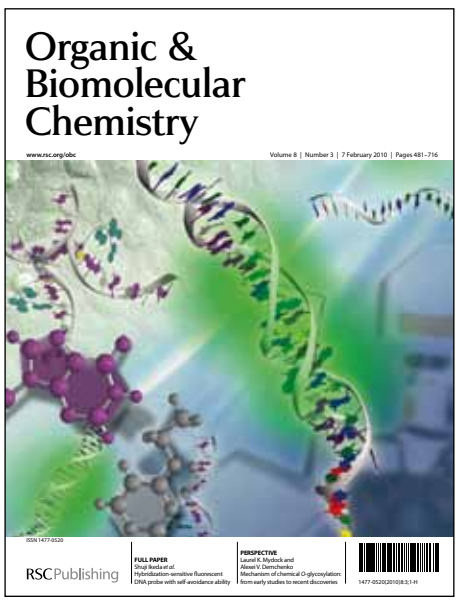


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ARTICLE TYPE

# Copper-catalyzed formation of *N,N*-dimethyl benzamide from nitrile and DMF under $O_2$ atmosphere

**Chenxu Hu,[a] Xufei Yan,[a] Xiangge Zhou,[a,b] Zhengkai Li[a]***

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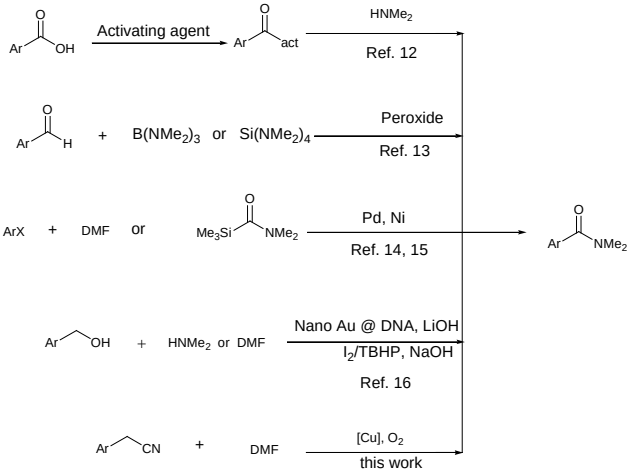
**Amidation of nitrile with *N,N*-dimethylformamide (DMF) was catalyzed by $Cu_2O$ with 1,10-phenanthroline as ligand under oxygen atmosphere. A variety of *N,N*-dimethyl benzamides were obtained in yields up to 84%.**

Amides, which can be found in many protein and peptide structures, are one of the most important functional groups in nature.[1] They are also important motifs in natural products, pharmaceuticals, agrochemicals and polymers.[2] Besides the classical synthetic method of activated acids with amine, several other catalytic protocols have been developed for their preparation. For example, Heck and coworkers firstly reported palladium-catalyzed synthesis of amides from alkenyl, aryl or heterocyclic halide with primary or secondary amines in the presence of carbon monoxide in 1974.[3] Following this pioneering work, different aminocarbonylation ways have been explored by using carbon monoxide as the source of carbonyl group.[4] To eliminate the cumbersome handling of toxic carbon monoxide gas, a great many of surrogates have then emerged, such as metal carbonyls like $W(CO)_6$,[5] $Mo(CO)_6$,[6] and $Ni(CO)_4$,[7] as well as other organic reagents like carbamoylsilane,[8] carbamoylstannanes,[9] formamide,[10] and DMF.[11] However, these substitutes usually have their own shortcomings such as high cost, thermal instability,[9] the necessity of using microwave etc.[11a] Moreover, most of these reactions still depend on palladium catalyst.

On the other hand, the traditional methods to synthesize *N,N*-disubstituted amides are limited by the necessity of preactivation of carboxylic acids,[12] oxidative amination of aldehydes,[13] cross-coupling of acyl chlorides in *N,N*-dimethylformamide,[14] aminocarbonylation or carbamoylation of aryl halides,[11,15] or direct amidation of alcohols[16] as shown in Scheme 1. Thus, low cost and simple way to obtain *N,N*-disubstituted amides are still challenging in synthetic organic chemistry.

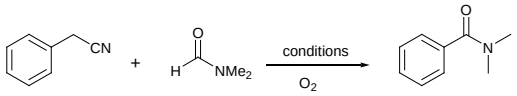
In continuation of our recent work of copper catalyzed C-CN bond cleavage,[17] herein is reported our recent work of copper-catalyzed amidation of nitriles by using DMF as an amide source.




**Scheme 1.** Synthetic methods of *N,N*-dimethyl amides

Initially, benzyl cyanide was chosen as model substrate to be reacted with DMF for the optimization of the reaction conditions by using benzyl cyanide (1 mmol), DMF (2 mL), $O_2$ atmosphere (1 atm.), base or acid (1 equiv.), Cu source (10 mol %) and ligand (20 mol %) at 140 °C for 24 h. As shown in Table 1, there was only trace of product to be detected in the absence of metal and molecular oxygen (Table 1, entries 1 and 2). Meanwhile, acid seemed to be better than base in this reaction. For example, *p*-toluenesulfonic acid gave yield around 44%, while acetic acid resulted in only 40% (Table 1, entries 2-6). Further control experiments indicated the necessity of addition of acid, and there was only trace of product to be found in the absence of it (Table 1, entry 4). Different copper sources were also examined, and $Cu_2O$ exhibited higher catalytic activities than others including $CuSO_4$, $Cu(OTf)_2$, $Cu(OAc)_2$ and CuO in the yield of 83% (Table 1, entries 6-13). Among the ligands screened, 1,10-phenanthroline was more beneficial for the reaction than others (Table 1, entries 13-16). Some other solvents were then tested, toluene, DMSO and $H_2O$ resulted in trace of product (Table 1, entries 19-21). Therefore, DMF is used as substrate as well as solvent in the following reactions. In addition, the effects of reaction temperatures of 120 °C, 140 °C were tested, and 140 °C was proved to be suitable for the reaction with 83% yield (Table 1, entries 12 and 17). After then, we shortened the reaction time from 24 h to 12 h, which lowered yield to 44% (Table 1, entry 18).

**Table 1.** Optimization of the reaction conditions.[a]



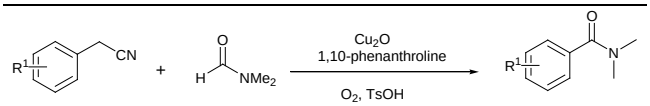

1a 2 3a

| Entry | Cu source | Ligand | Base or Acid | Yield[%] [b] |
|---|---|---|---|---|
| 1 | _ | Phen | TsOH | trace |
| 2 | $CuSO_4$ | Phen | TsOH | trace[c] |
| 3 | $CuSO_4$ | Phen | t-BuONa | Trace |
| 4 | $CuSO_4$ | Phen | _ | Trace |
| 5 | $CuSO_4$ | Phen | AcOH | 40 |
| 6 | $CuSO_4$ | Phen | TsOH | 44 |
| 7 | $Cu(OTf)_2$ | Phen | TsOH | 32 |
| 8 | $Cu(OAc)_2$ | Phen | TsOH | 57 |
| 9 | $Cu(OAc)_2$ | Phen | TsOH | 40 |
| 10 | CuO | Phen | TsOH | 47 |
| 11 | $CuSO_4$ | Phen | TsOH | 27 |
| 12 | $CuCl_2$ | Phen | TsOH | 15 |
| 13 | $Cu_2O$ | Phen | TsOH | 83 |
| 14 | $Cu_2O$ | 2-Picolinic acid | TsOH | 20 |
| 15 | $Cu_2O$ | 2-Nipecotic acid | TsOH | 30 |
| 16 | $Cu_2O$ | L-Proline | TsOH | 30 |
| 17 | $Cu_2O$ | Phen | TsOH | 56 [d] |
| 18 | $Cu_2O$ | Phen | TsOH | 44 [e] |
| 19 | $Cu_2O$ | Phen | TsOH | NR [f] |
| 20 | $Cu_2O$ | Phen | TsOH | NR[g] |
| 21 | $Cu_2O$ | Phen | TsOH | NR[h] |

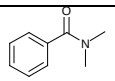
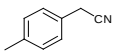
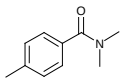
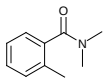
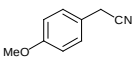
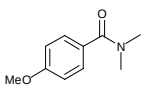
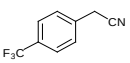
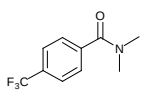
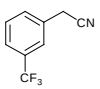
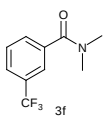
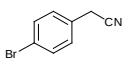
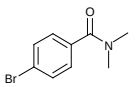
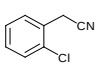
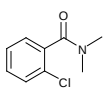
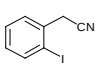
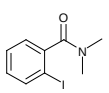
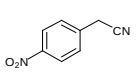
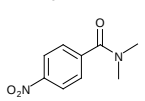
[a] Reaction conditions: 1.0 mmol of benzyl cyanide, 2 mL of DMF , $O_2$ (1 atm), 10 mol% Cu source, 20 mol% ligand, 1 mmol of base or acid unless otherwise indicated, 140 °C and 24h; Phen = 1,10-phenanthroline; TsOH= *p*-toluenesulfonic acid. [b] Isolated yields. [c] Performed under $N_2$. [d] Temperature was 120 °C. [e] 12 h. [f] 100 uL of DMF, toluene (2 mL) as solvent. [g] 100 uL of DMF, dimethylsulfoxide (2 mL) as solvent. [h] 100 uL of DMF, $H_2O$ (2 mL) as solvent.

Next, the scope of substrates was extended to various benzyl nitriles under the optimized reaction conditions: aryl nitriles (1 mmol), DMF (2 mL), TsOH (1 mmol), $Cu_2O$ (0.1 mmol) and 1,10-phenanthroline (0.2 mmol) at 140 °C for 24h. The results are listed in Table 2.

**Table 2.** Reaction of nitriles with DMF.[a]




1a - 1k 2 3a - 3k

| Entry | Reactant | Product | Yield(%)[b] |
|---|---|---|---|
| 1 |  |  3a | 83 |
| 2 |  |  3b | 81 |
| 3 |  |  3c | 68 |
| 4 |  |  3d | 79 |
| 5 |  |  3e | 81 |
| 6 |  |  3f | 84 |
| 7 |  |  3g | 78 |
| 8 |  |  3h | 64 |
| 9 |  |  3i | 53 |
| 10 |  |  3j | 76 |

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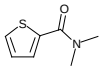
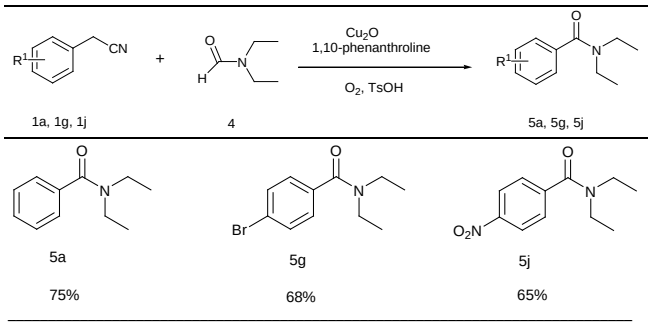
| 11 |  |  3k | 73 |

[a] Reaction conditions: 1.0 mmol of nitrile, 2 mL of DMF, $O_2$ (1 atm), 10 mol% $Cu_2O$, 20 mol% Phen, 1.0 mmol of TsOH, 140 °C and 24h. [b] Isolated yields.

In general, the electronic influences of substituents were not obvious, and benzyl nitriles bearing either electron-donating or electron-withdrawing groups were smoothly transformed to the corresponding products in yields ranging from 53% to 84% (Table 2, entries 2-11). On the contrary, the steric hindrance of the substituent had a significant effect on the results. For example, *p*-methylbenzyl cyanide gave the desired product in 81% yield, while *o*-methylbenzyl cyanide afforded the corresponding product in a relatively lower yield of 68% (Table 2, entries 2 and 3). Furthermore, the catalytic system could tolerate a variety of functionalized aryl nitriles in the reaction, including ether, nitro, trifluoromethyl, and halogen groups (Table 2, entries 2-10). Heterocyclic compounds, such as 2-thiopheneacetonitrile could also afford the corresponding products in 73% yield (Table 2, entry 11).

To further establish the general utility of this transformation, *N*,*N*-diethylformamide was also tried for this reaction with lower yields than the results of DMF, which indicated this protocol's potential usage in the synthesis of *N*-substituted amides (Table 3).

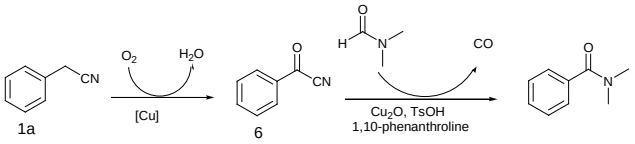
**Table 3.** Reaction of benzyl nitriles with DEF. [a]




[a] Reaction conditions: 1.0 mmol of benzyl cyanide, 2 mL of DEF, $O_2$ (1 atm), 10 mol% $Cu_2O$, 20 mol% 1,10-phenanthroline, 1.0 mmol of TsOH, 140 °C and 24 h. [b] Isolated yields.

At last, based on the literatures and our experimental results,[18] the possible reaction pathway was proposed as shown in Scheme 2. Firstly, benzyl cyanide 1a undergoes a copper-catalyzed oxidation with $O_2$ to generate 6.[19] Then, 6 forms product with *N*,*N*-dimethylamine, which is from the decomposition of DMF under the reaction conditions.[20] Furthermore, *N*,*N*-dimethylacetamide could also be reacted with benzyl cyanide, affording the same product in 80% yield.

Therefore, this reaction would contain the cleavage of C-CN bond of nitrile and C-N bond of DMF, and also contain new C-N bond formation of product.




**Scheme 2.** Proposed pathway for amide formation

In conclusion, we report here the preliminary studies into a copper-catalyzed C-C bond activation/amidation approach, which provides tertiary amides by coupling nitrile with DMF or DEF under oxygen atmosphere. This transformation offers an alternative method to prepare N-substituted amides and a new strategy for C-C bond cleavage.

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## Notes and references

[a] *Institute of Homogeneous Catalysis, College of Chemistry, Sichuan University, Chengdu 610064, People s Republic of China*
*Fax: (+86)-28-8541-2904; e-mail: zhengkaili@scu.edu.cn*
[b] *Key Laboratory of Organic Synthesis of Jiangsu Province, College of Chemistry, Chemical Engineering and Materials Science, Soochow University, Suzhou 215123, China*

† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

‡ Footnotes should appear here. These might include comments relevant to but not central to the matter under discussion, limited experimental and spectral data, and crystallographic data.

1 (a) R. C. Larock, *Comprehensive Organic Transformations*, 2nd ed. Wiley-VCH: Weinheim, 1999; (b) N. Sewald, H. D. Jakubke, *Peptides: Chemistry and Biology*; Wiley-VCH: Weinheim, 2002; (c) B. L. Bray, *Nat. Rev. Drug Discovery*, 2003, **2**, 587; (d) T. Cupido, J. Tulla-Puche, J. Spengler, F. Albericio, *Curr. Opin. Drug Discovery Dev.*, 2007, **10**, 768; (e) J. W. Bode, *Curr. Opin. Drug Discovery Dev.*, 2006, **9**, 765; (f) J. M. Humphrey, A. R. Chamberlin, *Chem. Rev.*, 1997, **97**, 2243.
2 J. M. Humphrey, A. R. Chamberlin, *Chem. Rev.*, 1997, **97**, 2243.
3 (a) A. Schoenberg, I. Bartoletti, R. F. Heck, *J. Org. Chem.*, 1974, 39, 3318; (b) A. Schoenberg, I. Bartoletti, R. F. Heck, *J. Org. Chem.*, 1974, **39**, 3327.
4 (a) X. F. Wu, H. Neumann, M. Beller, *Chem. Asian J.*, 2010, **5**, 2168; (b) P. J. Tambade, Y. P. Patil, B. M. Bhanage, *Appl. Organomet. Chem.*, 2009, **23**, 235; (c) A. Brennfuhrer, H. Neumann, M. Beller, *Angew. Chem., Int. Ed.*, 2009, **48**, 4114; (d) P. J. Tambade, Y. P. Patil, M. J. Bhanushali, B. M. Bhanage, *Synthesis*, 2008, **15**, 2347; (e) J. R. Martinelli, D. A. Watson, D. M. M. Freckmann, T. E. Barder, S. L. Buchwald, *J. Org. Chem.*, 2008, **73**, 7102; (f) J. R. Martinelli, T. P. Clark, D. A. Watson, R. H. Munday, S. L. Buchwald, *Angew. Chem. Int. Ed.*, 2007, **46**, 8460; (g) R. Skoda-Foldes, E. Takacs, J. Horvath, Z. Tuba, L. Kollar, *Green Chem.*, 2003, **5**, 643.
5 W. Ren, M. Yamane, *J. Org. Chem.*, 2009, **74**, 8332.
6 (a) A. Wieckowska, R. Fransson, L. R. Odell, M. Larhed, *J. Org. Chem.*, 2011, **76**, 978; (b) W. Ren, M. Yamane, *J. Org. Chem.*, 2010, **75**, 8410; (c) B. Roberts, D. Liptrot, L. Alcaraz, T. Luker, M. J. Stocks, *Org. Lett.*, 2010, **12**, 4280; (d) E. Ren, M. Yamane, *J. Org. Chem.*, 2010, **75**, 3017; (e) M. A. Letavic, K. S. Ly, *Tetrahedron Lett.*, 2007, **48**, 2339; (f) X. Wu, J. K. Ekegren, M. Larhed, *Organometallics*, 2006, **25**, 1434; (g) X. Wu, J. Wannberg, M. Larhed, *Tetrahedron*, 2006, **62**, 4665; (h) J. Wannberg, D. Dallinger, C. O. Kappe, M. Larhed, *J. Comb. Chem.*, 2005, **7**, 574; (i) J. Wannberg, N. K. Kaiser, dL. Vrang, B. Samuelsson, M. Larhed, A.

Hallberg, *J. Comb. Chem*., 2005, **7**, 611; (j) X. Wu, R. Ronn, T. Gossas, M. Larhed, *J. Org. Chem*., 2005, **70**, 3094; (k) K. Yamazaki, Y. Kondo, *J. Comb. Chem*., 2004, **6**, 121; (l) J. Wannberg, M. Larhed, *J. Org. Chem*., 2003, **68**, 5750; (m) J. Georgsson, A. Hallberg, M. Larhed, *J. Comb. Chem*., 2003, **5**, 350; (n) J. Wannberg, M. Larhed, *J. Org. Chem*., 2003, **68**, 5750; (o) N. K. Kaiser, A. Hallberg, M. Larhed, *J. Comb. Chem*., 2002, **4**, 109.

7 E. J. Corey, L. S. Hegedus, *J. Am. Chem. Soc*., 1969, **91**, 1233.

8 (a) R. F. Cunico, R. K. Pandey, *J. Org. Chem*., 2005, **70**, 9048; (b) R. F. Cunico, B. C. Maity, *Org. Lett.*, 2003, **5**, 4947; (c) R. F. Cunico, B. C. Maity, *Org. Lett*., 2002, **4**, 4357.

9 C. M. Lindsay, D. A. Widdowson,. *J. Chem. Soc., Perkin Trans*., 1988, 569.

10 Y. Wan, M. Alterman, M. Larhed, A. Hallberg, *J. Comb. Chem*., 2003, **5**, 82.

11 (a) Y. Jo, J. Ju, J. Choe, K. H. Song, S. Lee, *J. Org. Chem*., 2009, **74**, 6358; (b) J. Ju, M. Jeong, J. Moon, H. M. Jung, S. Lee, *Org. Lett*., 2007, **9**, 4615; (c) K. Hosoi, K. Nozaki, T. Hiyama, *Org. Lett*., 2002, **4**, 2849; (d) Y. Wan, M. Alterman, M. Larhed, A. Hallberg, *J. Org. Chem*., 2002, **67**, 6232.

12 E. Valeur, M. Bradley, *Chem. Soc. Rev.*, 2009, **38**, 606.

13 (a) K. Ekoue-Kovi, C. Wolf, *Chem. Eur. J*., 2008, **14**, 6302; (b) K. Ekoue-Kovi, C. Wolf, *Org. Lett*., 2007, **9**, 3429.

14 (a) F. Chen, B. Li, Q. Hu, L. Wang, Q. Lai, F. Li. *Organometallics*., 2011, **30**, 2026; (b) Coppinger, M. Galvin, *J. Am. Chem. Soc*., 1954, **76**, 1372.

15 (a) D. N. Sawant, Y. S. Wagh, K. D. Bhatte, B. M. Bhanage, *J. Org. Chem*., 2011, **76**, 5489; (b) R. F. Cunico, R. K. Pandey, *J. Org. Chem*., 2005, **70**, 9048; (c) R. F. Cunico, B. C. Maity, *Org. Lett*., 2003, **5**, 4947; (d) R. F. Cunico, B. C. Maity, *Org. Lett*., 2002, **4**, 4357.

16 (a) K. Xu, Y. Hu, S. Zhang, Z. Zha, Z. Wang. *Chem. Eur. J*., 2012, **18**, 9793; (b) Z. J. Liu, J. Zhang, S. L. Chen, E. B. Shi, Y. Xu, X. B. Wan, *Angew.Chem*., 2012, **124**, 3285; *Angew. Chem. Int. Ed*., 2012, **51**, 3231; (c) Q. Wang, C. F. Wan, Y. Gu, J. T. Zhang, L. F. Gao, Z. Y. Wang, *Green Chem*., 2011, **13**, 578; (d) Y. Z. Yan, Z. Y. Wang, *Chem. Commun*., 2011, **47**, 9513; (e) J. T. Zhang, D. P. Zhu, C. M. Yu, C. F. Wan, Z. Y. Wang, *Org. Lett*., 2010, **12**, 2841; (f) C. F. Wan, L. F. Gao, Q. Wang, J. T. Zhang, Z. Y. Wang, *Org. Lett*., 2010, **12**, 3902.

17 Z. Jiang, Q. Huang, S. Chen, L. Long, X. Zhou. *Adv. Synth. Catal*., 2012, **354**, 589.

18 To gain insight into the catalytic pathway of this reaction, a series of experiments were done (see supporting information): Firstly, the addition of 2,2,6,6-tetramethylpiperidin-1-yloxyl (TEMPO) into the reaction showed few effects on the results, which indicated that the reaction might not go through a radical process. Secondly, the GC-MS analysis of the reaction mixture showed the existence of CN-$NMe_2$, which further indicated the existence the cleavage of C-CN bond of nitrile and C-N bond of DMF.

19 S. Jin, D. Wen, P. Lu, G. Wang. *Chem. Commun*., 2012, **48**, 9933.

20 (a) S. T. Ding, N. Jiao. *Angew. Chem., Int. Ed.*, 2012, **51**, 9226; (b) Y. M. Li, Y. S. Xie, R. Zhang, K. Jin, X. N. Wang, C. Y. Duan, *J. Org. Chem*., 2011, **76**, 5444.