View Article Online
View Journal

ChemComm

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: X. Wu, Y. Li, C. wang, F. zhu, Z. wang, J.-F. Soule and P. H. Dixneuf, *Chem. Commun.*, 2016, DOI: 10.1039/C6CC08929A.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/chemcomm

View Article Online
DOI: 10.1039/C6CC08929A

Journal Name

COMMUNICATION

An Unexpected Copper-Catalyzed Carbonylative Acetylation of Amines

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

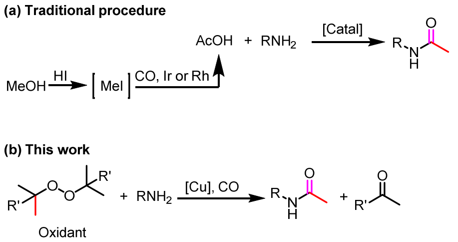
www.rsc.org/

Yahui Li+,[a] Changsheng Wang+,[b] Fengxiang Zhu,[a] Zechao Wang,[a] Jean François Soulé,[b] Pierre H. Dixneuf,[b] and Xiao-Feng Wu*[a]

A novel copper-catalyzed carbonylative acetylation of amines has been developed. With peroxide as the oxidant and methyl source copper catalyst under CO pressure lead to good yields of *N*-acetyl amides. Notably, this is the first example of carbonylative acetylation.

Acetylation of amine is one of the fundamental transformations in organic chemistry.[1] Additionally, its importance has also been verified by the numerous applications in pharmaceutical and agricultural industries.[2] Traditionally, acetylation of amines usually took place with acetic acid/acetic anhydride/acetyl chloride under either basic or acidic conditions (Scheme 1, eq. a).[3] Although acetylation with acetic acid represents the most straight forward procedure, however from the acetic acid synthesis point of view, chemical using acetic acid is mainly produced by carbonylation procedure (Cativa process and Monsanto process).[4] With methanol as the starting material under CO pressure and with Ir or Rh catalysts, acetic acid is produced in million tonnes per year. According to retrosynthetic analysis,[5] it should be possible and interesting to realize the application of carbonylation in acetylation. Nevertheless, the choice of methyl source is a challenge. With methyl iodide (the intermediate in Cativa process by reaction MeOH with HI) as the methyl source, methylation of amine via the nucleophilic substitution reaction between MeI and amine is much faster; with MeOH as the methyl source, the needed HI is not compatible with amine. Hence, no carbonylative acetylation has been developed until nowadays.

On the other hand, transitional metal-catalyzed carbonylative transformations have already become a powerful toolbox in modern organic synthesis.[6] With noble metals as the catalysts, CO can be easily introduced into the parent molecules. Taking consideration of the high price of noble metals and the required phosphine ligands, the exploration of non-noble catalysts for this area is a challenge and will be interesting. By looking at the catalytic behaviours and their advantages, copper catalysts will be a good option.[7] Indeed, copper catalysts are rarely applied in carbonylation reactions.[8,9] We recently studied the application of copper catalysts in carbonylative transformations of alkanes with amines and amides.[9] With copper as the catalyst and DTBP (di-*tert*-butyl peroxide) as the oxidant, amides or imides can be produced effectively from the corresponding alkanes and amines or amides. Interestingly, in some cases, acetylation of amine was observed during the optimization process. Under thermal conditions or in the presence of metal catalyst, peroxides can decompose into the corresponding alkoxy radical which could give a methyl radical through *β*-scission of alkoxy radical.[10] By analysis of the reaction conditions, we realized that the methyl group is from DTBP and trapped by CO to give the acetyl group. As the awareness of the importance of acetylation reaction and also the academic meaningfulness to use peroxide as methyl source in carbonylation, we focused on this transformation (Scheme 1, eq. b). In this procedure, peroxide acts both as oxidant and methyl source to give the first example of carbonylative acetylation.



Scheme 1. Acetylation methodologies.

With 1-octanamine as the model substrate, we established this catalytic system. With dicumyl peroxide[11] as the oxidant and methyl source, using CuF_2 (10 mol%) and 1,10-phenanthroline hydrate (1,10-phen.; 10 mol%) as the catalyst system, in chlorobenzene under pressure of CO at 140 °C, 79%

---

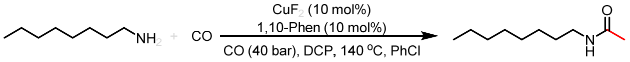
[a] Leibniz-Institut für Katalyse e.V. an der Universität Rostock; Albert-Einstein-Straße 29a, 18059 Rostock (Germany), E-mail: Xiao-Feng.Wu@catalysis.de
[b] Catalyse et Organométalliques, Institut Sciences Chimiques de Rennes, UMR 6226-CNRS-Université de Rennes, Av. Général Leclerc, 35042 Rennes (France)
+ These authors contributed equally to this work.

Electronic Supplementary Information (ESI) available: [General procedure, analytic data and NMR spectrums]. See DOI: 10.1039/x0xx00000x

View Article Online
DOI: 10.1039/C6CC08929A

of *N*-octylacetamide can be isolated (Table 1, entry 1). Only trace amount of acetamide can be detected in the absence of copper or ligand (Table 1, entries 2 and 3). Decreased reaction efficiency was observed in catalyst or ligands variation (Table 1, entries 4-6). And the decreasing of reaction temperature or CO pressure resulted in dropped yields of acetamide (Table 1, entries 7-9). DTBP is shown suitable reagent as well, 56% of *N*-octylacetamide was isolated (Table 1, entry 10); while no product can be detected with TBHP as the reagent (Table 1, entry 11).

Table 1. Optimization of reaction conditions.[a]

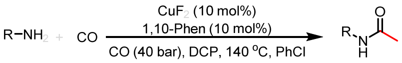


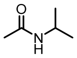
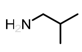
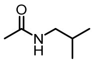
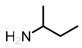
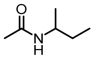
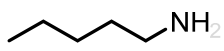
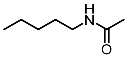
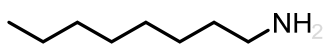
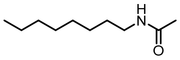
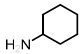
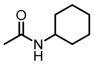
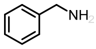
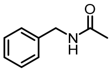
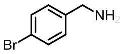
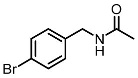
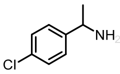
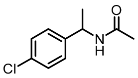
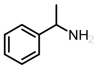
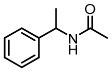
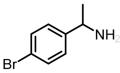
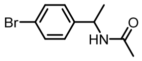
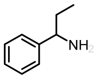
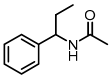
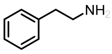
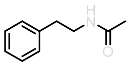
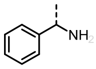
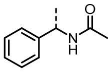
Entry	Variations from the standard conditions	Yield[b]
1	-	79%
2	Without CuF_2	trace
3	Without 1,10-Phen	trace
4	$CuBr(Me_2S)$ instead of CuF_2	31%
5	2,9-Dimethyl-1,10-phenanthroline instead of 1,10-Phen	61%
6	4,4′-Di-*tert*-butyl-2,2′-dipyridyl instead of 1,10-Phen	52%
7	100 °C, 20 bar CO	48%
8	120 °C, 20 bar CO	55%
9	20 bar CO	67%
10	DTBP instead of DCP	56%
11	TBHP instead of DCP	0

[a] 1-Octanamine (0.5 mmol), catalyst (10 mol%), ligand (10 mol%), 1 mmol DCP, 40 bar CO, PhCl (2 mL), 24 h. [b] Isolated yields, the yields were calculated based on the amount of amine applied. TBHP: *t*-Butyl hydroperoxide solution 70 wt. % in H_2O. DCP: Dicumyl peroxide. DTBP: Di-*tert*-butyl peroxide. 1,10-Phen: 1,10-Phenanthroline hydrate.

With the best reaction conditions in hand (Table 1, entry 1), we performed substrates testing of this novel procedure (Table 2). Good to excellent yields of acetamides can be produced with the tested alkyl amines (Table 2, entries 1-6).

Table 2. Cu-catalyzed carbonylative acetylation of amines.[a]



Entry	$R-NH_2$	Product	Yield[b]
1			80%
2			71%
3			89%
4			77%
5			79%
6			90%
7			59%
8			65%
9			60%
10			75%
11			74%
12			72%
13			81%
14			80%

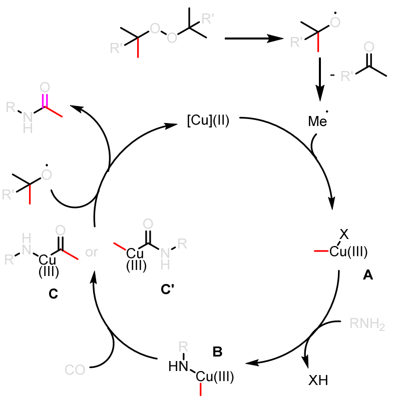
[a] Amine (0.5 mmol), CuF_2 (10 mol%), 1,10-phen. (10 mol%), 1 mmol DCP, 40 bar CO, PhCl (2 mL), 140 °C, 24 h. [b] Isolated yields, the yields were calculated based on the amount of amine applied.

Benzylic and other aromatic substituted amines are proven to be suitable substrates as well; moderate to good yields can be obtained in general (Table 2, entries 7-14). The chirality of the starting amine kept, and good yield of the acetylated product can be isolated (Table 2, entry 14). Additionally, aniline was tested as well. Around 30% of *N*-phenylacetamide was obtained and together with aniline oxidized products.

Based on our results, a possible reaction mechanism is proposed (Scheme 2). The reaction started with a copper(II)-catalyzed or thermal hemolytic cleavage of a peroxide to

View Article Online
DOI: 10.1039/C6CC08929A

generate the corresponding alkoxy radical. A methyl radical will be generated through *β*-scission of the alkoxy radical, which reacts with copper(II) species to give the corresponding Cu(III)-methyl species A. Then complex A reacts with amine through X ligand exchange to produce Cu(III) intermediate B. Followed by CO insertion forms the intermediate C or C', which will give the final carbonylation product after reductive elimination. Meanwhile, the formed Cu(I) intermediate reacted with alkoxy radical to produce Cu(II) species for the next catalytic cycle.



Scheme 2. Proposed reaction pathway.

Conclusions

In conclusion, an interesting copper-catalyzed carbonylative acetylation of amines has been developed. With peroxide as the oxidant and also methyl source, good yields of *N*-acetyl amides were formed from the corresponding amines. Notably, this is the first example on carbonylative acetylation.

Notes and references

Acknowledgements: The authors thank the Chinese Scholarship Council for financial Support. The analytic supports of Dr. W. Baumann, Dr. C. Fisher, S. Buchholz, and S. Schareina are gratefully acknowledged. We also appreciate the generous support from Professor Matthias Beller in LIKAT.

General Procedure: A 4 mL screw-cap vial was charged with CuF_2 (5.05 mg, 10 mol%), 1,10-phenanthroline hydrate (9.9 mg, 10 mol%) and an oven-dried stirring bar. The vial was closed by Teflon septum and phenolic cap and connected with a needle. After amine (0.5 mmol), DCP (1 mmol) and PhCl (2 mL) were injected by syringe, the vial was fixed in an alloy plate and put into Paar 4560 series autoclave (300 mL) under argon atmosphere. At room temperature, the autoclave is flushed with carbon monoxide for three times and 40 bar of carbon monoxide was charged. The autoclave was placed on a heating plate equipped with magnetic stirring and an aluminium block. The reaction is allowed to be heated under 140 °C for 24 hours. Afterwards, the autoclave is cooled to room temperature and the pressure was carefully released. After removal of solvent under reduced pressure, pure product was obtained by column chromatography on silica gel (eluent: pentane/ethyl acetate = 1:1).

1 a) R. C. Larock, *Comprehensive Organic Transformations*, 2nd ed.; VCH: Weinheim, Germany, 1989; b) T. W. Greene, P. G. M. Wuts, *Protective Groups in Organic synthesis*, 3rd ed.; John Wiley & Sons, Inc.: New York, 1999.
2 a) J. M. Humphrey, A. R. Chamberlin, *Chem. Rev.* 1997, **97**, 2243; b) A. Scozzafava, T. Owa, A. Mastrolorenzo, C. T. Supuran, *Curr. Med. Chem.* 2003, **10**, 925; c) J. S. Carey, D. Laffan, C. Thomson, M. T. Williams, *Org. Biomol. Chem.* 2006, **4**, 2337; d) F. Abbate, C. T. Supuran, A. Scozzafava, P. Orioli, M. T. Stubbs, G. Klebe, *J. Med. Chem.* 2002, **45**, 3583.
3 a) A. Vogel, *Practical Organic Chemistry*; Langman Scientific & Technical and Wiley: New York, 1989; b) J. March, *Advanced Organic Chemistry*, 4th ed.; John Wiley & Sons: New York, 1992.
4 a) J. H. Jones, *Platinum Metals Rev.* 2000, **44**, 94; b) G. J. Sunley, D. J. Watson, *Catal. Today* 2000, **58**, 293.
5 a) E. J. Corey, *Chem. Soc. Rev.* 1988, **17**, 111; b) E. J. Corey, *Angew. Chem. Int. Ed.* 1991, **30**, 455.
6 For selected recent reviews on carbonylation reaction, see: a) X. F. Wu, H. Neumann, M. Beller, *Chem Rev* 2013, **113**, 1; b) X. F. Wu, H. Neumann, M. Beller, *Chem. Soc. Rev.* 2011, **40**, 4986; c) X.-F. Wu, H. Neumann, *ChemCatChem* 2012, **4**, 447; d) Q. Liu, H. Zhang, A. Lei, *Angew. Chem. Int. Ed.* 2011, **50**, 10788; e) X. F. Wu, H. Neumann, M. Beller, *ChemSusChem* 2013, **6**, 229; f) C. H. Schiesser, U. Wille, H. Matsubara, I. Ryu, *Acc. Chem. Res.* 2007, **40**, 303; g) S. Sumino, A. Fusano, T. Fukuyama, I. Ryu, *Acc. Chem. Res.* 2014, **47**, 1563; h) B. Gabriele, R. Mancuso, G. Salerno, *Eur. J. Org. Chem.* 2012, 6825; i) S. D. Friis, A. T. Lindhardt, T. Skrydstrup, *Acc. Chem. Res.* 2016, **49**, 594.
7 S. E. Allen, R. R. Walvoord, R. Padilla-Salinas, M. C. Kozlowski, *Chem. Rev.* 2013, **113**, 6234.
8 a) J. M. Liu, R. Z. Zhang, S. F. Wang, W. Sun, C. G. Xia, *Org. Lett.* 2009, **11**, 1321; b) P. Tambade, Y. Patil, N. Nandurkar, B. Bhanage, *Synlett* 2008, 886; c) S.-K. Kang, T. Yamaguchi, T.-H. Kim, P.-S. Ho, *J. Org. Chem.* 1996, **61**, 9082.
9 a) Y. Li, K. Dong, F. Zhu, Z. Wang, X.-F. Wu, *Angew. Chem. Int. Ed.* 2016, **55**, 7227; b) Y. Li, F. Zhu, Z. Wang, X.-F. Wu, *ACS Catal.* 2016, **6**, 5561.
10 P. Gray, A. Williams, *Chem. Rev.* 1959, **59**, 239.
11 T. Kubo, N. Chatani, *Org. Lett.* 2016, **18**, 1698.