

Chlorine-free copper-catalyzed oxidative synthesis of 1,3,4-oxadiazoles with molecular oxygen as the sole oxidant*

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Abstract: Chlorine-free is not only one of the new concepts of green chemistry, but also a problematical task for chemical processes in industrial utility. During the past several decades, we devoted ourselves to the study of chlorine-free organic synthesis. Herein, we describe an efficient chlorine-free copper-catalyzed oxidative approach providing 1,3,4-oxadiazoles in good yields from readily available starting materials. This transformation requires only a green and inexpensive reagent to afford the structurally useful motifs, and has a broad functional groups tolerance.

Keywords: chlorine-free; copper; cyclizations; heterocyclic chemistry; 1,3,4-oxadiazoles; oxidation; oxygen; synthesis.

INTRODUCTION

During the past several decades, transition-metal-catalyzed transformations of readily available starting materials to various functionalized organic molecules have become the most important area in organic synthesis. Among these processes, copper-catalyzed reactions, such as Glaser coupling [1], Cadiot–Chodkiewicz coupling [2], and Ullmann coupling [3,4] have caused much attention because they not only provide an efficient carbon–carbon bond-forming method, but also have been widely used in the synthesis of advanced materials, pharmaceutical products, and natural products. Besides, copper salts are generally used as cocatalysts or reoxidants of palladium catalyst for Wacker oxidation [5], Sonogashira coupling [6], etc. Based on copper as an inexpensive and nontoxic metal, the study on the transformations of readily available starting materials to various functionalized organic molecules in the presence of copper will be of great importance and attract more and more attention.

In 1999, we demonstrated for the first time that Glaser coupling can be carried out in the presence of copper chloride (CuCl_2) in supercritical carbon dioxide (scCO_2) using NaOAc instead of amines, and the amount of CuCl_2 was 2 equiv of the substrate [7]. At the same period, we also reported that CuCl_2 was employed as an efficient cocatalyst/reoxidant to accomplish the Pd(II)-catalyzed carbonylation of norbornene in scCO_2 [8]. Later, we found that the Wacker reaction of 1-octene, and the similar oxidative reaction (acetalization reaction) of terminal olefins bearing electron-withdrawing groups can be carried out smoothly in the presence of CuCl or CuCl_2 as the cocatalyst in methanol-modified scCO_2 [9,10]. Based on these results, we developed a few synthetic methods with use of cop-

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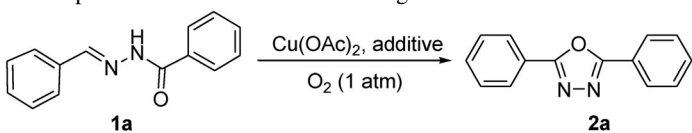
per salts as cocatalyst/reoxidant in conventional organic solvents or in $scCO_2$, such as the PdX_2/CuX_2 -catalyzed carbonylation reactions of alkynes in alcohol-benzene solvent [11–16], the $PdCl_2/CuCl_2$ -catalyzed carbonylation of amines in $scCO_2$ [17], the cyclotrimerization of alkynes in alcohol-benzene or in MeOH-modified $scCO_2$ in the presence of $PdCl_2/CuCl_2$ [18–20], the $PdCl_2/CuCl_2$ -catalyzed allylation of alkynes with allyl alcohols in aqueous media [21,22], and so on.

According to Anastas's principles for green chemistry, the general areas include selections of feedstocks, reagents, solvents, reaction conditions, and catalysts, and the design of safer chemicals [23]. Actually, chlorine-free is not only one of the new concepts of green chemistry, but also a problematical task for the chemical process in industrial utility. In order to solve this problem, two routes were chosen in our group. The first one is to replace $CuCl_2$ or $CuCl$ with other chlorine-free cocatalyst/reoxidant. We employed polystyrene-supported benzoquinone (PS-BQ), hydroquinone (PS-HQ), or PS-phenol as an efficient cocatalyst with palladium catalyst for the Wacker reaction in $scCO_2$, and the reaction can tolerate electron-withdrawing groups, i.e., acrylate esters, acrylonitrile, methyl vinyl ketone, and acrolein [24–27]. Further studies showed that molecular oxygen is quite an environmentally friendly and efficient oxidant in palladium catalytic systems [28–37]. The other one is to use or design chlorine-free copper catalyst for the reaction [38,39]. In this context, we continued to study chlorine-free copper-catalyzed transformations of readily available starting materials to various functionalized organic molecules. And we report our findings herein.

RESULTS AND DISCUSSION

Oxazoles are common structural motifs found in numerous molecules that display antiviral, antifungal, antibacterial, and antiproliferative activities [40,41]. The potential biological activity and the prevalence of oxazoles in both natural products and pharmaceuticals have inspired significant interest in the synthesis of these heterocycles [42–44]. 1,3,4-Oxadiazoles [45,46] are of particular interest, owing to their various biological activities [47–50] and optical and charge-transporting properties [51]. They are also a blocking group of electrochemically active materials [52] and, as well, can be used as binucleating ligands for generating bimetallic complexes [53]. To date, many synthetic methods have been developed to construct the oxazole skeleton, however, some of them usually present significant limitations, such as tedious work-up and the harsh nature of reaction conditions, involving stoichiometric quantities of oxidants which would produce a large amount of by-products, or even toxic reagents, such as PbO_2 [54] and I(III) salt [55] waste matters.

We started our study by examining the conversion of *N'*-benzylidenebenzohydrazide **1a** into 2,5-diphenyl-1,3,4-oxadiazole **2a**. After an initial screen of additives, solvents, and reaction temperature, we found that the use of 10 mol % of $Cu(OAc)_2$ in dimethylformamide (DMF) at 80 °C under an oxygen atmosphere after 12 h produced **2a** in 35 % yield with a low conversion of **1a** (Table 1, entry 1). We then selected base additives, such as K_2CO_3 , pyridine, Et_3N , and DABCO (1,4-diazabicyclo[2.2.2]octane) to improve this transformation (Table 1, entries 2–5), and found that DABCO was the best base to promote the reaction. Loading 30 mol % of DABCO converted the starting material into the product completely, and afforded **2a** in 90 % isolated yield. Solvent also plays an important role to this transformation, and DMF was tested as the best (Table 1, entry 3 vs. entries 6–11). The reaction at lower temperature gave a lower yield (Table 1, entry 12).

Table 1 Optimization of the initial screening results^a.


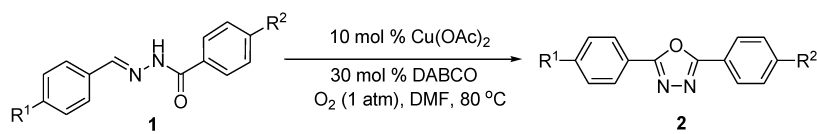
Entry	Additive	Solvent	T (°C)	Yield ^b (%)
1	–	DMF	80	35
2	Pyridine	DMF	80	65
3	DABCO	DMF	80	95 (90)
4	K ₂ CO ₃	DMF	80	74
5	Et ₃ N	DMF	80	86
6	DABCO	DMSO	80	80
7	DABCO	DMA	80	85
8	DABCO	Toluene	80	76
9	DABCO	DCE	80	69
10	DABCO	1,4-Dioxane	80	63
11	DABCO	H ₂ O	80	27
12	DABCO	DMF	60	65

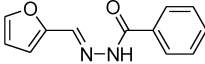

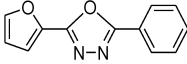
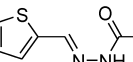

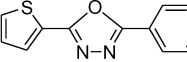
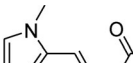

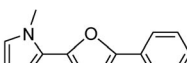
^aReaction conditions: **1a** (0.5 mmol), catalyst (5 mol %), additive (30 mol %), solvent (3 mL), the reaction was carried out at the given temperature for 12 h in sealed tube.

^bDetermined by GC. Number in parentheses is isolated yield.

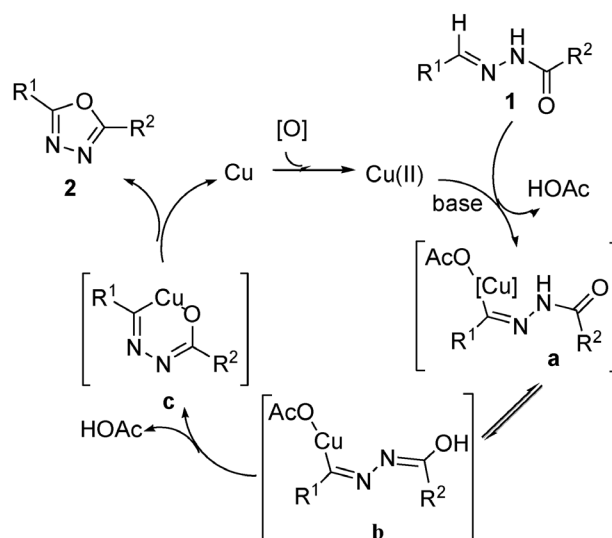
With the optimized conditions at hand, we next explored the scope and generality of the process. Derivatives of **1** were prepared through the addition of an ester to a hydrazine and an aldehyde derivative following known procedures [56,57]. As shown in Table 2, a variety of substituents R¹, R² on substrate **1** all led to the desired products in moderate to good yields. Especially, strong electron-withdrawing groups of R¹, such as CF₃ and F, gave the promised products in excellent yields (Table 2, entries 8, 9).

Compound **1** with heterocyclic substituents also proceeded smoothly to afford the corresponding 1,3,4-oxadiazoles (Table 2, entries 10–12), which could be expanded to be applied in a broader synthetic and materials area. The ability to incorporate the whole range of halogen substituents (Table 2, entries 5–8 and 14) makes this method particularly appealing, since these substituents could be used for further synthetic manipulations.

Table 2 Synthesis of substituted 1,3,4-oxadiazoles.


Entry	R ¹	R ²	Yield of 2 (%)
1	H	H	2a (90)
2	<i>o</i> -OMe	H	2b (81)
3	<i>p</i> -OMe	H	2c (88)
4	<i>m</i> -NO ₂	H	2d (92)
5	<i>m</i> -Br	H	2e (83)
6	<i>o</i> -Br	H	2f (82)
7	<i>p</i> -Br	H	2g (90)
8	<i>p</i> -F	H	2h (93)
9	<i>p</i> -CF ₃	H	2i (94)
10			 2j (86)
11			 2k (87)
12			 2l (89)
13	2-mesityl	H	2m (78)
14	<i>p</i> -Br	<i>o</i> -Br	2n (88)

We currently are unsure of the mechanistic course of the oxadiazole-forming process. Scheme 1 outlines possible pathways suggested by the literature precedent of related processes. The reaction of **1** with Cu(OAc)₂ presumably leads to **a** with the aid of base additives, while copper either in oxidation state II or III [58]. Isomerization of **a** into **b**, following by the OH attacks the copper center in **b** to give a metallacycle **c** [59]. Product **2** is subsequently formed through reductive elimination of the metal with molecular oxygen to realize the Cu(II) reborn and the catalytic cycles.



Scheme 1 Possible reaction pathways for the conversion of **1** into **2**.

CONCLUSIONS

We herein report an efficient chlorine-free copper-catalyzed oxidative approach providing 1,3,4-oxadiazoles in good yields from readily available starting materials. This transformation requires only a green and inexpensive reagent to obtain the structurally useful motifs, and has a broad functional groups tolerance. More importantly, chlorine-free synthesis in this work is fit for very demanding requirements of green chemistry, and shows its potential utilization in chemical processes.

SUPPLEMENTARY INFORMATION

Supplementary Information is available online (doi:10.1351/PAC-CON-11-07-04).

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REFERENCES

1. C. Glaser. *Ber. Dtsch. Chem. Ges.* **2**, 422 (1969).
2. W. Chodkiewicz. *Ann. Chim.* **2**, 819 (1957).
3. F. Ullmann. *Ann.* **332**, 38 (1904).
4. F. Ullmann, P. Sponagel. *Ber.* **38**, 2211 (1905).
5. J. Tsuji. *Synthesis* **5**, 369 (1984).
6. K. Sonogashira, Y. Tohda, N. Hagira. *Tetrahedron Lett.* **50**, 4467 (1975).
7. J. Li, H. Jiang, L. Jia. *Chem. Commun.* **23**, 2369 (1999).
8. L. Jia, H. Jiang, J. Li. *Green Chem.* **1**, 91 (1999).
9. H. Jiang, L. Jia, J. Li. *Green Chem.* **2**, 161 (2000).

10. L. Jia, H. Jiang, J. Li. *Chem. Commun.* **23**, 985 (1999).
11. J. Li, H. Jiang, A. Feng, L. Jia. *J. Org. Chem.* **64**, 5984 (1999).
12. J. Li, H. Jiang, M. Chen. *Tetrahedron Lett.* **42**, 6923 (2001).
13. J. Li, H. Jiang, L. Jia. *Synth. Commun.* **29**, 3733 (1999).
14. J. Li, H. Jiang, M. Chen. *Synth. Commun.* **31**, 199 (2001).
15. J. Li, H. Jiang, M. Chen. *Synth. Commun.* **31**, 3131 (2001).
16. J. Li, H. Jiang, M. Chen. *Chin. J. Chem.* **19**, 689 (2001).
17. J. Li, H. Jiang, M. Chen. *Green Chem.* **3**, 137 (2001).
18. J. Li, H. Jiang, M. Chen. *J. Org. Chem.* **66**, 3627 (2001).
19. J. Cheng, H. Jiang. *Eur. J. Org. Chem.* **3**, 643 (2004).
20. J. Cheng, J. Li, H. Jiang, X. Ouyang, Q. Zhang. *Synth. Commun.* **33**, 3003 (2003).
21. J. Huang, L. Zhou, H. Jiang. *Angew. Chem., Int. Ed.* **45**, 1945 (2006).
22. H. Jiang, C. Qiao, W. Liu. *Chem.—Eur. J.* **16**, 10968 (2010).
23. P. Anastas, T. Williamson. *Green Chemistry*, Oxford University Press, New York (1998).
24. Z. Wang, H. Jiang, C. Qi, Y. Wang, H. Liu. *Green Chem.* **7**, 582 (2005).
25. Z. Wang, H. Jiang, X. Ouyang, C. Qi, S. Yang. *Tetrahedron* **62**, 9846 (2006).
26. Z. Wang, H. Jiang, C. Qi, Y. Shen, S. Yang, Y. Zeng. *Chin. J. Catal.* **26**, 607 (2007).
27. Z. Wang, H. Jiang, C. Qi, Y. Shen, S. Yang. *Chin. Chem. Lett.* **18**, 969 (2007).
28. H. Jiang, Y. Shen, Z. Wang. *Tetrahedron Lett.* **48**, 7542 (2007).
29. H. Jiang, Y. Shen, Z. Wang. *Tetrahedron* **64**, 508 (2008).
30. A. Wang, H. Jiang. *J. Am. Chem. Soc.* **130**, 5030 (2008).
31. A. Wang, H. Jiang, H. Chen. *J. Am. Chem. Soc.* **131**, 3846 (2009).
32. A. Wang, H. Jiang. *J. Org. Chem.* **75**, 2321 (2010).
33. H. Jiang, H. Chen, A. Wang, X. Liu. *Chem. Commun.* **46**, 7259 (2010).
34. Y. Shen, H. Jiang, Z. Chen. *J. Org. Chem.* **75**, 1321 (2010).
35. P. Zhou, L. Huang, H. Jiang, A. Wang, X. Li. *J. Org. Chem.* **75**, 8279 (2010).
36. P. Zhou, H. Jiang, L. Huang, X. Li. *Chem. Commun.* **47**, 1003 (2011).
37. P. Zhou, M. Zhen, H. Jiang, X. Li, C. Qi. *J. Org. Chem.* **76**, 4759 (2011).
38. L. Huang, H. Jiang, C. Qi, X. Liu. *J. Am. Chem. Soc.* **132**, 17652 (2010).
39. H. Cao, H. Jiang, Y. Yuan, Z. Chen, C. Qi, H. Huang. *Chem.—Eur. J.* **16**, 10553 (2010).
40. D. C. Palmer (Ed.). *Oxazoles: Synthesis, Reactions and Spectroscopy*, Part A, John Wiley, Hoboken, NJ (2003).
41. D. C. Palmer (Ed.). *Oxazoles: Synthesis, Reactions and Spectroscopy*, Part B, John Wiley, Hoboken, NJ (2004).
42. Z. Jin. *Nat. Prod. Rep.* **23**, 464 (2006).
43. V. S. C. Yeh. *Tetrahedron* **60**, 11995 (2004).
44. P. Wipf. *Chem. Rev.* **95**, 2115 (1995).
45. G. W. Weaver. In *Science of Synthesis*, Vol. 13, R. C. Storr, T. L. Gilchrist (Eds.), pp. 219–251, Thieme, Stuttgart (2004).
46. J. Hill. In *Comprehensive Heterocyclic Chemistry II*, Vol. 4, R. C. Storr (Ed.), pp. 267–287, 905–1006, Pergamon, Oxford (1996).
47. Q. Chen, X. L. Zhu, L. L. Jiang, Z. M. Liu, G. F. Yang. *Eur. J. Med. Chem.* **43**, 595 (2008).
48. R. B. Shankar, R. G. Pews. *J. Heterocycl. Chem.* **30**, 169 (1993).
49. F. A. Omar, N. M. Mahfouz, M. A. Rahman. *Eur. J. Med. Chem.* **31**, 819 (1996).
50. S. Perez, B. Lasheras, C. Oset, A. Carmen. *J. Heterocycl. Chem.* **34**, 1527 (1997).
51. P. K. Hegde, A. V. Adhikari, M. G. Manjunatha, C. S. S. Sandeep, P. Reji. *Synth. Met.* **159**, 1099 (2009).
52. C. C. Chiang, H. C. Chen, C. Lee, M. Leung, K. R. Lin, K. H. Hsieh. *Chem. Mater.* **20**, 540 (2008).
53. C. J. Qin, A. L. Gavrilova, B. Bosnich. *Inorg. Chem.* **40**, 1386 (2001).

54. K. C. Chiang, F. F. Wong, C. H. Hung, Y. Y. Huang, P. W. Chang, Y. M. Liao, S. K. Lin. *J. Heterocycl. Chem.* **46**, 111 (2006).
55. C. Dobrota, C. C. Paraschivescu, I. Dumitru, M. Matache, I. Baci, L. L. Ruta. *Tetrahedron Lett.* **50**, 1886 (2009).
56. A. Husain, A. Ahmad, M. M. Alam, Mohd Ajmal, P. Ahuja. *Eur. J. Med. Chem.* **44**, 3798 (2009).
57. S. Rostamizadeh, S. A. G. Housaini. *Tetrahedron Lett.* **45**, 8753 (2004).
58. For a discussion of mechanisms involving Cu(III) intermediates, see: S. V. Ley, A. W. Thomas. *Angew. Chem., Int. Ed.* **42**, 5400 (2003).
59. For a report suggesting a Cu metallacycle as intermediate, see: K. Yamada, T. Kubo, H. Tokuyama, T. Fukuyama. *Synlett* **2**, 231 (2002).