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Copper(II)-mediated formation of oxazole-4-carbonitrile from acetophenone and coordinated cyanide anion *via* a radical coupling†

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A protocol for the direct synthesis of 5-aryloxazole-4-carbonitrile from acetophenone was first described with potassium ferricyanide as a cheap and low toxicity cyanide reagent, in which, multiple bond formation was implemented *via* an oxygen mediated radical mechanism. Potassium ferricyanide played a dual role as a "CN" source and also as a coupling partner for the cyclization of oxazole.

Oxazole derivatives, one of the most important heterocyclic compounds, are widely present in natural products,¹ synthesized drugs² and advanced materials.³ Meanwhile, a significant proportion of drugs used in clinical treatment contain a cyano group.⁴ In addition, the introduction of a cyano group to small-molecule lead compounds is one of the most critical strategies in drug development because the cyano group can be easily converted into amide, carboxylic acid, imido ester, amidine, and methyl ammonia groups.^{5,6} Thus, the introduction of a cyano group to an oxazole ring is an appealing idea.

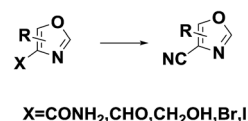
Over the years, many strategies for the preparation of cyano-oxazoles have been developed, which includes the dehydration of carboxamides to nitriles,^{7–9} nucleophilic substitution on oxazoles¹⁰ and intramolecular condensation of β -acyloxyenamines (Scheme 1).¹¹ These methods suffered from harsh reaction conditions, toxic reagents or unavailable starting materials. Herein, exploring the potential of non-toxic and efficient systems is imperative, which might provide a smooth approach to construct carbonitrile from ubiquitously present substrates.

Initially, the authors tried to develop an efficient cyano substitution reaction *via* C–H bond activation¹² with acetophenone as the substrate using nontoxic cyanide sources, such as potassium ferricyanide and potassium ferrocyanide (Scheme 2). Quite incidentally, 5-phenyloxazole-4-carbonitrile was obtained dramatically in the presence of CuI₂ and Pd(OAc)₂ with DMF as solvent (Scheme 2). The surprising results aroused our interesting and the reaction was investigated further. Subsequently,

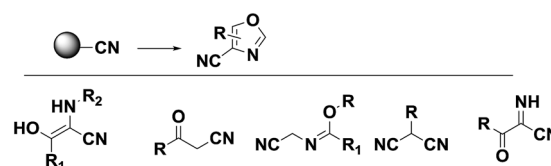
we found that 5-phenyloxazole-4-carbonitrile was obtained smoothly in the absence of Pd(OAc)₂.

To gain a better understanding of this attractive result, we systematically studied the function of oxidants and cyanide (Table 1). At the beginning of the investigation, the reaction of acetophenone (**1a**), DMF, and potassium ferricyanide was examined in the presence of CuI₂ (1.0 equiv.) at 130 °C for 12 h. The expected 5-phenyloxazole-4-carbonitrile (**2a**) was obtained in 29% yield with the formation of side product *N,N*-dimethyl-2-oxo-2-phenylacetamide¹³ in 19% yield, and 40% of raw material was recovered (Table 1, entry 1). The reaction did not occur in the absence of CuI₂ or K₃[Fe(CN)₆] (entries 2 and 3). The other oxidants such as CuI, FeBr₃ and ZnBr₂ were investigated (entries 4–10). The yield of **2a** was up to 75% when CuBr₂ was used as the oxidant (entry 10). It was found out that the effects of Cu(II) salts and Fe(III) salts was superior to Cu(I) salts in the system. Organic oxidants, such as NBS, were tested to enhance the conversion of this reaction. However, only inferior conversion was observed (entries 12). The use of KCN, CuCN or K₄[Fe(CN)₆] instead of K₃[Fe(CN)₆] also led to the formation (entry 15–17), but only

a) Cyanation of oxazole precursors



b) Cyclization of the substrate containing ready-made "CN"



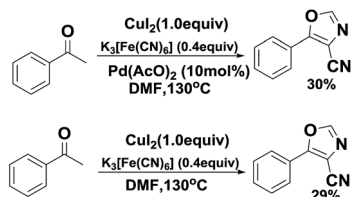
Scheme 1 Synthesis of oxazole-4-carbonitrile.

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Scheme 2 A surprising result.

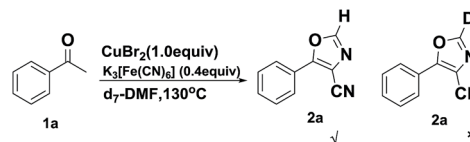
Table 1 Optimization of the reaction conditions^a

Entry	Oxidant	Cyanide	Yield ^b (%)
1	CuI ₂	K ₃ Fe(CN) ₆	29
2	—	K ₃ Fe(CN) ₆	NR
3	CuI ₂	—	NR
4	CuCl	K ₃ Fe(CN) ₆	NR
5	CuI	K ₃ Fe(CN) ₆	Trace
6	FeBr ₃	K ₃ Fe(CN) ₆	40
7	ZnBr ₂	K ₃ Fe(CN) ₆	NR
8	CuCl ₂	K ₃ Fe(CN) ₆	50
9	CuBr	K ₃ Fe(CN) ₆	NR
10	CuBr ₂	K ₃ Fe(CN) ₆	75
11	CuO/I ₂	K ₃ Fe(CN) ₆	26
12	NBS	K ₃ Fe(CN) ₆	Trace
15	CuBr ₂	CuCN	39
16	CuBr ₂	KCN	70
17	CuBr ₂	K ₄ Fe(CN) ₆	43
18 ^c	CuBr ₂	K ₃ Fe(CN) ₆	NR
19 ^d	CuBr ₂	K ₃ Fe(CN) ₆	71

^a Reaction conditions: **1a** (1.0 mmol), K₃[Fe(CN)₆] (0.4 mmol) or KCN (2.0 mmol) or CuCN (2.0 mmol), DMF (3 mL), oxidant (1.0 mmol), at 130 °C. ^b Isolated yield. ^c Nitrogen atmosphere. NR: no desired product was detected. ^d Oxygen balloon.

using KCN showed good result (entry 16). From the safety and yield point of view, K₃[Fe(CN)₆] was chosen as the cyanide source. Interestingly, in an exclusive nitrogen atmosphere, the transformation was shut down (entry 18), which indicated that O₂ play a crucial role in the reaction. In addition, when the reaction was performed under an O₂ atmosphere, the result was the same as that under an air atmosphere (entry 19).

Next, we turned our attention to the effect of solvent on the reaction. It turned out that 5-phenyloxazole-4-carbonitrile was not detected when DMF was replaced with other solvents, such as acetonitrile, dimethyl sulfoxide, *N*-methyl-2-pyrrolidone or ethylene glycol, which indicated that the DMF is indispensable in the reaction. Considering that DMF has the capability to participate in the reaction,¹⁴ a control experiment with DMF-d₇ as the solvent was carried out (Scheme 3). 5-Phenyloxazole-4-carbonitrile-2-d was not detected, which means that DMF participate in this reaction only as an excellent solvent involving coordinated cyanide anion.^{12a,15} Meanwhile, it turned out that

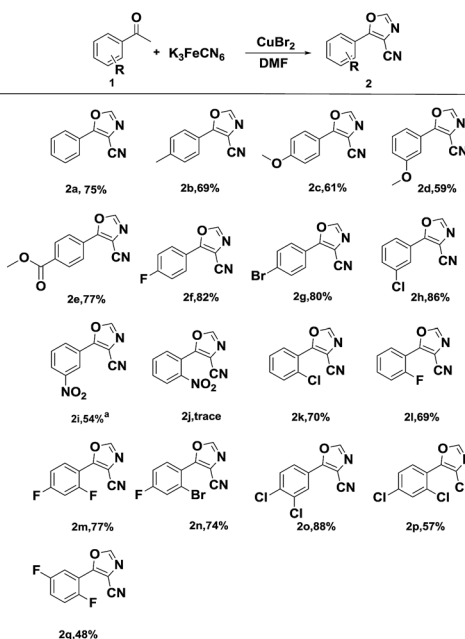


Scheme 3 Control experiments for investigating the role of DMF.

the “CN” in K₃[Fe(CN)₆] also participated in the cyclization rather than DMF.

With the optimized conditions in hand (Table 1, entry 10), the scope of substrates for the reaction was explored. The structures and yields of the products are summarized in Scheme 4.

Almost all of the starting acetophenones bearing mono-substitution or poly-substitution were successfully transformed into the desired 4-carbonitrile products in moderate to good yields. In addition, the electronic properties of the substituents on the aromatic ring significantly influenced the efficiency of this transformation. The reactions of 4-fluoro, 4-bromo, and 3-chloro acetophenone proceeded smoothly to afford the corresponding products (**2f–2h**) in excellent yields. Furthermore, the optimized reaction conditions were also applicable to acetophenones with the electron-donating substituents (**2b–2d**). However, the strong electron-withdrawing groups on acetophenone, such as –NO₂, hindered the conversion (**2i** and **2j**) and the reaction required a high temperature. A low yield was observed in the case of 2-substituted acetophenones (**2j–2l**) due to the influence of steric hindrance. Besides, the reactions of methyl 4-acetylbenzoate proceeded smoothly to afford the corresponding products (**2e**), while, the starting acetophenones bearing aldehydes^{18a} or acids were hardly transformed into the desired 4-carbonitrile products.

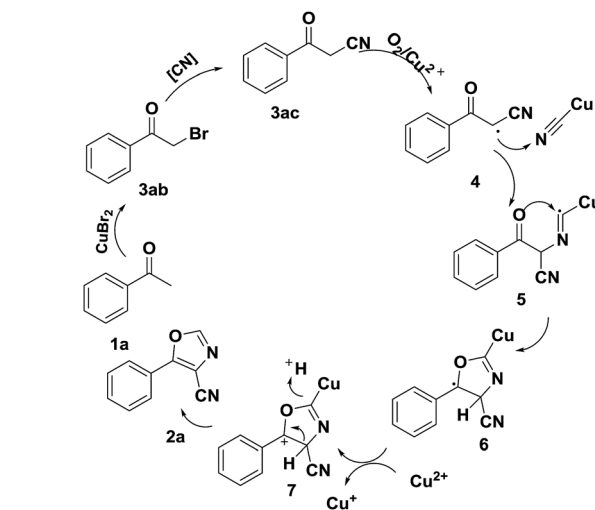
Scheme 4 Scope of acetophenones. Reaction conditions: **1a** (1.0 mmol), K₃[Fe(CN)₆] (0.4 mmol), DMF (3 mL), CuBr₂ (1.0 mmol), at 130 °C. Isolated yield. ^aAt 140 °C.

Subsequently, in order to gain insight into the reaction mechanism, several control experiments were performed as shown in Scheme 5. We proposed a plausible reaction pathway involving the formation of an intermediate, such as 2-bromo-1-phenylethan-1-one (**3ab**) and 3-oxo-3-phenylpropanenitrile (**3ac**) *via* halogenation¹⁶ and nucleophilic reaction.¹⁷ In subsequent experiments, both **3ab** and **3ac** transformed to the desired **2a** in a comparative yields, which implied that the transfer undergo the halogenation and nucleophilic process. Furthermore, ethyl benzoylacetate could converse to the desired ethyl 5-phenyloxazole-4-carboxylate in this system (**2ac**).

In addition, it is noteworthy that the reaction was inhibited in the presence of radical scavengers, suggesting the possibility of a radical pathway (Scheme 6).

On the base of experimental results and according to previous studies,^{16–20} a possible reaction mechanism is proposed and shown in Scheme 7. Firstly, acetophenone transferred to 3-oxo-3-phenylpropanenitrile (**3ac**) *via* halogenation¹⁴ and nucleophilic¹⁵ reaction in the presence of CuBr_2 and $\text{K}_3[\text{Fe}(\text{CN})_6]$. Next, Cu^{II} served as a single electron oxidant to convert the **3ac** to the radical species **4**.¹⁸ The $\text{Cu}^{\text{I}}\text{CN}^{18a}$ species then combines with radical species **4** to generate the Cu^{I} -bonded radical intermediate **5**. Immediately, intermediate **5** transformed to the radical intermediate **6** *via* cyclization,¹⁹ which was oxidized by Cu^{II} to form the cationic intermediate **7**.²⁰ Finally, the desired product **2a** is obtained from **7** *via* elimination reaction.

In conclusion, an efficient, low-toxicity formation of 5-aryloxazole-4-carbonitrile from acetophenone was developed using potassium ferricyanide as a cyanide reagent with $\text{Cu}(\text{II})$ bromide as an oxidant, in which, potassium ferricyanide played a dual role as a “CN” source and also as a coupling partner for the cyclization of oxazole. The reaction conditions are mild and suitable for a wide range of substrates. Most of these substrates, such as 4-fluoro, 3-chloro, and 4-bromo acetophenone, provide

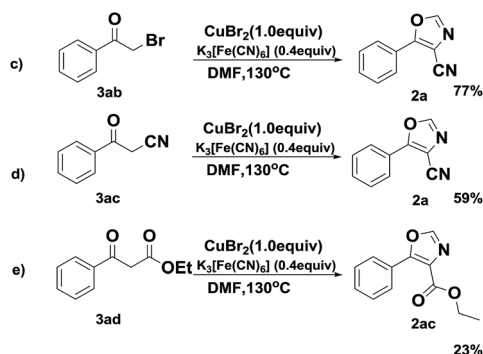


Scheme 7 Proposed mechanism.

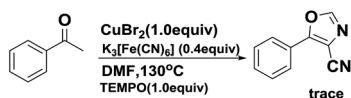
the corresponding products in moderate to excellent yields. In addition, the dramatic multiple bond formation provides a practical one-pot access to various 5-aryloxazole-4-carbonitrile derivatives from accessible raw materials. In addition, a reasonable reaction mechanism was proposed.

Notes and references

- (a) W. Wang, D. Yao, M. Gu, M. Fan, J. Li, Y. Xing and F. Nan, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 5284; (b) N. Desroy, F. Moreau, S. Briet, G. Le Fralliec, S. Floquet, L. Durant, V. Vongsouthi, V. Gerusz, A. Denis and S. Escaich, *Bioorg. Med. Chem.*, 2009, **17**, 1276; (c) S. Heng, K. R. Gryncel and E. R. Kantrowitz, *Bioorg. Med. Chem.*, 2009, **17**, 3916; (d) D. S. Dalisay, E. W. Rogers, A. S. Edison and T. F. Molinski, *Nat. Prod.*, 2009, **72**, 732; (e) Z. Jin, *Nat. Prod. Rep.*, 2009, **26**, 382; (f) Z. Jin, *Nat. Prod. Rep.*, 2011, **28**, 1143.
- (a) S. Heng, K. R. Gryncel and E. R. Kantrowitz, *Bioorg. Med. Chem.*, 2009, **17**, 3916; (b) D. S. Dalisay, E. W. Rogers, A. S. Edison and T. F. Molinski, *Nat. Prod.*, 2009, **72**, 732; (c) N. Desroy, F. Moreau, S. Briet, G. Le-Fralliec, S. Floquet, L. Durant, V. Vongsouthi, V. Gerusz, A. Denis and S. Escaich, *Bioorg. Med. Chem.*, 2009, **17**, 1276; (d) S. Heng, K. R. Gryncel and E. R. Kantrowitz, *Bioorg. Med. Chem.*, 2009, **17**, 3916.
- (a) A. Reiser, L. J. Leyshon, D. Saunders, M. V. Mijovic, A. Bright and J. Bogie, *J. Am. Chem. Soc.*, 1972, **94**, 2014; (b) T. Toyooka, H. P. Chokshi, R. S. Givens, R. G. Carlson, S. M. Lunte and T. Kuwana, *Biomed. Chromatogr.*, 1993, **7**, 208.
- (a) M. El-Kemary, J. A. Organero, L. Santos and A. J. Douhal, *J. Phys. Chem. B*, 2006, **110**, 14128; (b) C. A. Hughes, L. Robinson, A. Tseng and R. D. MacArthur, *Expert Opin. Pharmacother.*, 2009, **10**, 2445; (c) Y. Fradet, *Expert Rev. Anticancer Ther.*, 2004, **4**, 37; (d) E. Teodori, S. Dei, A. Garnier-Suillerot, F. Gualtieri, D. Manetti, C. Martelli,



Scheme 5 Control experiments for investigating the possible intermediates for the reaction.



Scheme 6 Control experiments for investigating the reaction type.



- M. N. Romanelli, S. Scapecchi, P. Sudwan and M. Salerno, *J. Med. Chem.*, 2005, **48**, 7426.
- 5 (a) Y. Ju, F. Liu and C. Li, *Org. Lett.*, 2009, **11**, 3582; (b) J. X. Qiao, X. Cheng, D. P. Modi, K. A. Rossi, J. M. Luetzgen, R. M. Knabb, P. K. Jadhav and R. R. Wexler, *Bioorg. Med. Chem. Lett.*, 2005, **15**, 29; (c) Z. Rappoport, *The Chemistry of the Cyano Group*, Interscience Publishers: London, 1970.
- 6 F. F. Fleming, L. H. Yao, P. C. Ravikumar, L. Funk and B. C. Shook, *J. Med. Chem.*, 2010, **53**, 7902.
- 7 (a) W. Bonrath, *Ultrason. Sonochem.*, 2003, **10**, 55; (b) B. K. Srivastava, R. Soni, A. Joharapurkar, K. V. Sairam, J. Z. Patel, A. Goswami, S. A. Shedage, S. S. Kara, S. P. Salunke, S. B. Gugale, A. Dhawas, P. Kadam, B. Mishra, N. Sadhwanid, V. B. Unadkatd, P. Mitrad, M. R. Jainb and P. R. Patel, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 963.
- 8 (a) F. A. Romero, I. Hwang and D. L. Boger, *J. Am. Chem. Soc.*, 2006, **128**, 14004; (b) F. A. Romero, W. Du, I. Hwang, T. J. Rayl, F. S. Kimball, D. Leung, H. S. Hoover, R. L. Apodaca, J. G. Breitenbucher, B. F. Cravatt and D. L. Boger, *J. Med. Chem.*, 2007, **50**, 1058; (c) F. Aquino, R. Karge, H. Pauling and W. Bonrath, *Molecules*, 1997, **2**, 176.
- 9 (a) J. Linder, T. P. Garner, H. E. Williams, M. S. Searle and C. J. Moody, *J. Am. Chem. Soc.*, 2011, **133**, 1044; (b) J. K. DeMartino, J. Garfinkle, D. G. Hochstatter, B. F. Cravatt and D. L. Boger, *Bioorg. Med. Chem. Lett.*, 2008, **18**, 5842; (c) H. Wada, H. E. Williams and C. J. Moody, *Angew. Chem., Int. Ed.*, 2015, **54**, 15147; (d) V. M. Prokopenko, S. G. Pil'ov, A. N. Vasilenko and V. S. Brovarets, *Russ. J. Gen. Chem.*, 2010, **80**, 2358.
- 10 (a) D. Haas, M. Mosrin and P. Knochel, *Org. Lett.*, 2013, **15**, 6162; (b) K. Burger, E. Hoss and K. Geith, *Synthesis*, 1990, **4**, 360.
- 11 (a) X. Liu, R. Cheng, F. Zhao, D. Zhang-Negrerie, Y. Du and K. Zhao, *Org. Lett.*, 2012, **14**, 5282; (b) I. K. Khanna, Y. Yu, R. M. Huff, R. M. Weier, X. Xu, F. J. Koszyk and J. L. Masferrer, *J. Med. Chem.*, 2000, **43**, 3168; (c) K. Matsumura, O. Miyashite, H. Shimadzu and N. Hashimoto, *Chem. Pharm. Bull.*, 1976, **24**, 948; (d) T. P. Sycheva, T. K. Trupp and M. N. Shchukina, *Zh. Obshch. Khim.*, 1962, **32**, 1071; (e) J. W. Cornforth and H. T. Huang, *J. Chem. Soc.*, 1948, 1969; (f) F. Freeman and D. S. Kim, *Tetrahedron Lett.*, 1989, **30**, 2631.
- 12 (a) X. F. Jia, D. P. Yang, W. H. Wang, F. Luo and J. Cheng, *J. Org. Chem.*, 2009, **74**, 9470; (b) G. Yan, C. Kuang, Y. Zhang and J. Wang, *Org. Lett.*, 2010, **12**, 1052; (c) Y. Ren, M. Yan, S. Zhao, J. Wang, J. Ma, X. Tian and W. Yin, *Adv. Synth. Catal.*, 2012, **354**, 2301.
- 13 (a) W. P. Mai, H. H. Wang, Z. C. Li, J. W. Yuan, Y. M. Xiao, L. R. Yang, P. Mao and L. B. Qu, *Chem. Commun.*, 2012, **48**, 10117; (b) Q. Zhao, T. Miao, X. Zhang, W. Zhou and L. Wang, *Org. Biomol. Chem.*, 2013, **11**, 1867.
- 14 (a) J. Xiao, Q. Li, T. Chen and L. B. Han, *Tetrahedron Lett.*, 2015, **43**, 5937; (b) L. Zhang, P. Lu and Y. Wang, *Org. Biomol. Chem.*, 2015, **30**, 8322; (c) J. Kim, H. Kim and S. Chang, *Org. Lett.*, 2012, **14**, 3924; (d) S. Ding and N. Jiao, *J. Am. Chem. Soc.*, 2011, **133**, 12374.
- 15 (a) O. Grossman and D. Gelman, *Org. Lett.*, 2006, **8**, 1189; (b) Y. Z. Zhu and C. Cai, *Synth. Commun.*, 2008, **38**, 2753; (c) Y. Ren, Z. Liu, S. He, S. Zhao, J. Wang, R. Niu and W. Yin, *Org. Process Res. Dev.*, 2009, **13**, 764; (d) G. Yan, C. Kuang, Y. Zhang and J. Wang, *Org. Lett.*, 2010, **12**, 1052.
- 16 R. Aeluri, M. Alla, S. Polepalli and N. Jain, *Eur. J. Med. Chem.*, 2015, **100**, 18.
- 17 (a) S. Eagon, N. Ball-Jones, D. Haddenham, J. Saavedra, C. DeLieto, M. Buckman and B. Singaram, *Tetrahedron Lett.*, 2010, **51**, 6418; (b) S. Kamila, D. Zhu, E. R. Biehl and L. Hua, *Org. Lett.*, 2006, **8**, 4429.
- 18 (a) Q. Wu, Y. Luo, A. Lei and J. You, *J. Am. Chem. Soc.*, 2016, **138**, 2885; (b) S. E. Allen, R. R. Walvoord, R. Padilla-Salinas and M. C. Kozlowski, *Chem. Rev.*, 2013, **113**, 6234; (c) G. G. Melikyan, *Org. React.*, 1997, **49**, 427.
- 19 (a) Y. Yamamoto, M. Ohno and S. Eguchi, *J. Org. Chem.*, 1996, **61**, 9264; (b) R. S. Liu, S. M. Ghorpade and P. D. Jadhav, *Chem.-Eur. J.*, 2016, **22**, 2915; (c) C. Chatgililoglu, D. Crich, M. Komatsu and I. Ryu, *Chem. Rev.*, 1999, **8**, 1991; (d) H. Ishibashi, M. Higuchi, M. Ohba and M. Ikeda, *Tetrahedron Lett.*, 1998, **39**, 75.
- 20 (a) G. Qin, X. Chen, L. Yang and H. Huang, *ACS Catal.*, 2015, **5**, 2882; (b) T. Nishikata, Y. Noda, R. Fujimoto and T. Sakashita, *J. Am. Chem. Soc.*, 2013, **135**, 16372.

