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PII: S0040-4039(14)02022-X
DOI: http://dx.doi.org/10.1016/j.tetlet.2014.11.108
Reference: TETL 45492

To appear in: *Tetrahedron Letters*

Received Date: 5 September 2014
Revised Date: 18 November 2014
Accepted Date: 23 November 2014

Please cite this article as: Li, Y., Shi, D., Zhu, P., Jin, H., Li, S., Mao, F., Shi, W., Copper mediated oxidative coupling between terminal alkynes and CuCN, *Tetrahedron Letters* (2014), doi: http://dx.doi.org/10.1016/j.tetlet.2014.11.108

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Copper Mediated Oxidative Coupling between Terminal Alkynes and CuCN

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Abstract

A direct oxidative cross coupling between terminal alkynes and CuCN to form 1-cyanoalkynes was reported. FeCl3 was employed as the sole additive. The reaction could be carried out under mild conditions, with moderate to good yields.

Keywords
iron; cyanoalkyne; oxidative coupling; terminal alkyne

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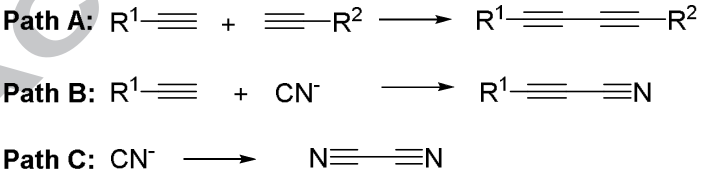
Oxidative coupling reactions have been an important synthetic route in the latest decades.[1] Tremendous efforts have been devoted to this area and great achievements have been made. Of these examples, bonding between two *sp* hybridized carbon centers may be the earliest oxidative coupling reactions since 1869, by Carl Glaser.[2] Besides, there are at least two other forms of oxidative C*sp*-C*sp* coupling reactions, as described in Scheme 1. Path A shows the most common form, the coupling between two terminal alkynes (or alkynyl metallic reagents). Typical procedure include the Cu(I) catalyzed Glaser-Eglinton-Hay homocoupling reactions.[3] It is noteworthy that C*sp* species are not limited to alkynes, but should also include the cyano group.[1c] Path B and Path C have shown other possibilities of C*sp*-C*sp* type oxidative couplings involving cyano groups.

Scheme 1 Possible forms of oxidative coupling reactions between two C*sp* centers



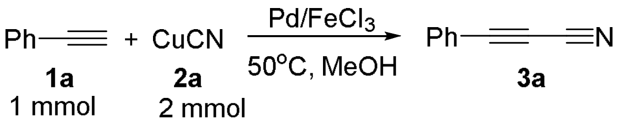
Path B in Scheme 1 has represented a new synthetic strategy towards the cyanoalkynes, an important structure in both synthetic and mechanistic studies.[4] Cyanoalkynes have also constituted a prominent homologous series of complex interstellar molecules identified by radioastronomy.[5] To the best of our knowledge, only a few reports have focused on the synthesis of cyanoalkynes. Xie and Kato have reported a method from aldehyde through biosynthesis.[6] Gough and Trippett have reported the synthesis through pyrolysis.[7] Apart from these methods, the direct cross coupling of terminal alkynes with cyano groups would be more efficient.

Ricci *et al.* reported one example of the bis(trimethylsilyl)peroxide (BTMSPO) promoted reaction of phenylacetylene with CuCN.[8] In this report, 30% of homo-coupled 1,4-diphenyl-1,3-butadiyne was formed, which limited its application. Luo *et al*. have reported the iodide-catalyzed cyanation of terminal acetylenes with CuCN in the presence of excess chlorotrimethylsilane (TMSCl).[9] 10 mol% of NaI and 3 eq. of TMSCl as well as CuCN were required to obtain the cyanoalkynes in moderate to good yields. Recently, Okamoto *et al.* have used cyanogen iodide as cyanation reagent.[10] However, BTMSPO, cyanogen iodine or other cyanogroup sources are usually toxic, expensive or difficult to handle in laboratories, and the excessive use of them may limit the application of these methods therefore.

Inspired by the concept of oxidative coupling, we have started the investigation of direct oxidative coupling between terminal alkynes and the relatively low toxic CuCN (due to the low K_{sp}) to form the cyanoalkynes. At first, we have used 2 mmol% of $Pd(OAc)_2$ as catalyst with 2 eq. of CuCN to investigate the reactions. After 3 days in MeOH under 50°C, 33% of the desired product was obtained. Other solvents, including toluene, DMSO, MeCN and amine systems showed less reactivity, as the low solubility of iron salts in them.

We have then optimized the reaction conditions, as shown in Table 1. It is shown that 6 hours was enough for the reaction. Increasement of Pd catalyst loading did not improve the yield obviously. It was noteworthy that considerable yield of cyanoalkyne was obtained *without* the addition of Pd salt (entry 9, table 2). More importantly, 1,4-diphenyl-1,3-butadiyne, a commonly observed byproduct in terminal alkynes involved systems, was not determined in this case without Pd salt. This discovery indicated us that Pd was not necessary for this reaction.

Table 1 Cyanoalkynes from terminal alkynes[a]

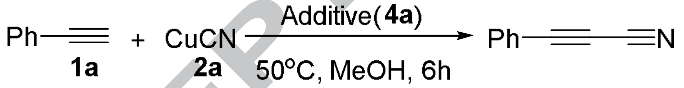


Entry	$Pd(OAc)_2$	$FeCl_3$	t(h)	Yield(%)[b]
1	0.1	3	7	35
2	0.05	3	7	41
3	0.05	3	2	37
4	0.05	3	4	44
5	0.05	3	6	54
6	0.05	3	8	47
7	0.02	2	7	46
8	0.02	3	7	53
9	0	3	17	34

[a] All reactions were carried out in 2mL solvent. [b] Based on **1a**, GC yieds, diphenyl as the internal standard.

Further investigations were then carried out without Pd catalyst. Considering the toxicity of CuCN, we have used excess of alkynes to promote the transformation of CuCN, as shown in Table 2. Different additives were explored, while sole $FeCl_3$ under air atmosphere (Entry 6, Table 2) performed the best.

Table 2 Different additives[a]



Entry	**4a**	**1a/2a**	**4a/2a**	Yield (%)[b]
1	$FeCl_3$	3	3	62
2	$FeCl_3$/air	3	3	69
3[c]	$FeCl_3$	1/3	1	24[d]
4	Ag_2O	3	3	-
5	$FeBr_3$/air	3	3	trace
6[e]	$FeCl_3$/air	3	3	71

[a] 1 mmol **2a** were used. [b] Based on **2a**, GC yields using diphenyl as internal standard. [c] 1 mmol **1a** was used. [d] Based on **1a**. [e] Reaction was carried out under 60°C.

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We have then applied this oxidative cross coupling method to various terminal alkynes. Table 3 has listed the preliminary results. Moderate to good yields were observed in both electron rich and poor aryl alkynes. Importantly, among all these reactions, diynes were almost not determined even under the air atmosphere. 1-chloroalkynes were determined as the main byproduct and could be easily removed by column chromatography. It is also interesting that **3h** was obtained in high yield, which has a longer C*sp* chain. However, aliphatic alkynes showed relatively low activity under this condition, with less than 40% of isolated yields (entry 12, Table 3. For 1-octyne, only trace product was observed).

Table 3 Oxidative coupling using different alkynes[a]

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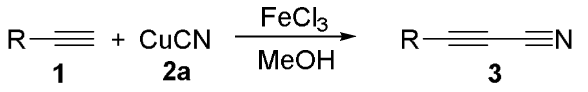
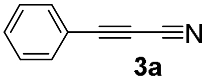
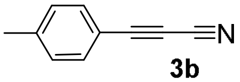
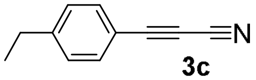
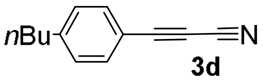
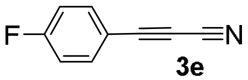
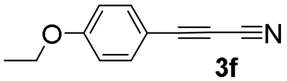
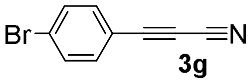
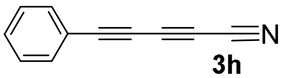
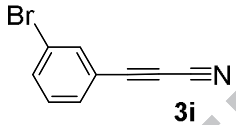
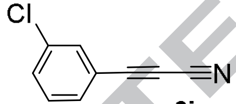
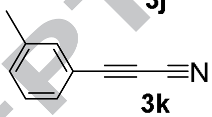
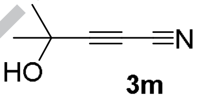


Entry	Product	Yield(%)[b]
1	 **3a**	71(69)
2	 **3b**	63(54)
3	 **3c**	70(50)
4	 **3d**	67(33)
5	 **3e**	58(35)
6	 **3f**	54(21)
7	 **3g**	56(41)
8	 **3h**	81
9	 **3i**	41(45)
10	 **3j**	48
11	 **3k**	61(48)
12	 **3m**	38(15)

[a] 3 mmol **1** and 1 mmol **2a** were used under 50°C, MeOH as solvent. [b] Isolated yields. The yields in parentheses are carried out using 3 eq. of CuCN and 1 eq. of alkynes.

In further studies, we have found that 1-chloroalkynes do not react with CuCN under this condition, indicating that they do not act as the intermediate. No reaction occurs under this condition in the absence of iron or copper. Interestingly, 30% of 1-chloroalkynes was observed when catalytic amount of CuCN (10%) was added to the system. Further investigations including broader substrate scope and detailed mechanism studies are currently carrying out in our team and more results will be reported in due course.

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In conclusion, an Iron-mediated oxidative coupling between terminal alkynes and CuCN to form the cyanoalkynes under mild reaction conditions was discovered. Low cost could be achieved since $FeCl_3$ was employed as the sole additive and the reaction may be carried out in air. This method provides an efficient way to form cyanoalkynes, which will greatly promote the studies in this research area.

Acknowledgments

This work was supported by NSFC (21202050) and the Natural Science Foundation of Hubei Province of China (2014CFB930).

References

1. (a) Liu, Q.; Jackstell, R.; Beller, M. *Angew. Chem., Int. Ed.* **2013,** *52*, 13871; (b) Li, B.-J.; Shi, Z.-J. *Chem. Soc. Rev.* **2012,** *41*, 5588; (c) Shi, W.; Liu, C.; Lei, A. *Chem. Soc. Rev.* **2011,** *40*, 2761; (d) Liu, C.; Zhang, H.; Shi, W.; Lei, A. *Chem. Rev.* **2011,** *111*, 1780; (e) Liu, C.; Jin, L.; Lei, A. *Synlett* **2010**, 2527.
2. Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000,** *39*, 2632.
3. Shi, W.; Lei, A. *Tetrahedron Lett.* **2014,** *55*, 2763.
4. (a) Yamamoto, Y.; Asatani, T.; Kirai, N. *Adv. Synth. Catal.* **2009,** *351*, 1243; (b) Reutenauer, P.; Kivala, M.; Jarowski, P. D.; Boudon, C.; Gisselbrecht, J.-P.; Gross, M.; Diederich, F. *Chem. Commun.* **2007**, 4898; (c) Kuznetsov, M. L.; Nazarov, A. A.; Kozlova, L. V.; Kukushkin, V. Y. *J. Org. Chem.* **2007,** *72*, 4475; (d) Cordiner, R. L.; Corcoran, D.; Yufit, D. S.; Goeta, A. E.; Howard, J. A. K.; Low, P. J. *Dalton Trans.* **2003**, 3541.
5. (a) Halter, R. J.; Fimmen, R. L.; McMahon, R. J.; Peebles, S. A.; Kuczkowski, R. L.; Stanton, J. F. *J. Am. Chem. Soc.* **2001,** *123*, 12353; (b) McCarthy, M. C.; Grabow, J. U.; Travers, M. J.; Chen, W.; Gottlieb, C. A.; Thaddeus, P. *Astrophys. J.* **1998,** *494*, L231; (c) Eichler, D. *Nature* **1982,** *295*, 391.
6. Xie, S.-X.; Kato, Y.; Asano, Y. *Biosci., Biotechnol., Biochem.* **2001,** *65*, 2666.
7. Gough, S. T. D.; Trippett, S. *J. Chem. Soc.* **1962**, 2333.
8. Casarini, A.; Dembech, P.; Reginato, G.; Ricci, A.; Seconi, G. *Tetrahedron Lett.* **1991,** *32*, 2169.
9. (a) Luo, F.-T.; Wang, M.-W.; Wang, R. T. *Org. Synth.* **1998,** *75*, 146; (b) Luo, F. T.; Wang, R. T. *Tetrahedron Lett.* **1993,** *34*, 5911.
10. Okamoto, K.; Watanabe, M.; Sakata, N.; Murai, M.; Ohe, K. *Org. Lett.* **2013,** *15*, 5810.

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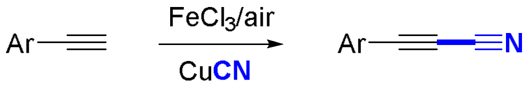
Graphic Abstract:



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