Copper-catalyzed direct cyanation of terminal alkynes with benzoyl cyanide

Yan Du, Zheng Li

PII: S0040-4039(18)31386-8
DOI: https://doi.org/10.1016/j.tetlet.2018.11.049
Reference: TETL 50434

To appear in: *Tetrahedron Letters*

Received Date: 30 September 2018
Revised Date: 13 November 2018
Accepted Date: 19 November 2018

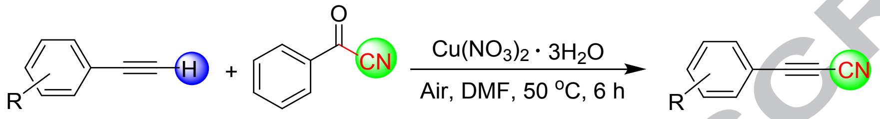
Please cite this article as: Du, Y., Li, Z., Copper-catalyzed direct cyanation of terminal alkynes with benzoyl cyanide, *Tetrahedron Letters* (2018), doi: https://doi.org/10.1016/j.tetlet.2018.11.049

Graphical Abstract

Copper-catalyzed direct cyanation of terminal alkynes with benzoyl cyanide

Leave this area blank for abstract info.

Yan Du, Zheng Li*



- Air as an oxidant
- Mild condition
- Less toxic cyanating agent

ELSEVIER

Tetrahedron Letters
journal homepage: www.elsevier.com

Copper-catalyzed direct cyanation of terminal alkynes with benzoyl cyanide

Yan Du, Zheng Li*

College of Chemistry and Chemical Engineering, Northwest Normal University, Lanzhou, Gansu, 730070, P. R. China

ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

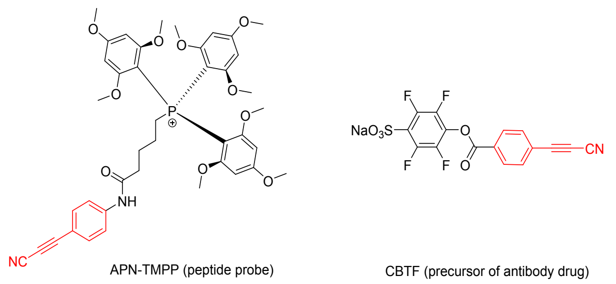
Keywords:
Terminal alkyne
Benzoyl cyanide
Cyanation
Propiolonitrile

ABSTRACT

Copper-catalyzed direct cyanation of terminal alkynes is achieved using less toxic, stable and easy to handle benzoyl cyanide as a cyanide source and air as an oxidant. This protocol provides a good alternative to the preparation of 3-arylpropiolonitriles under mild condition.

Introduction

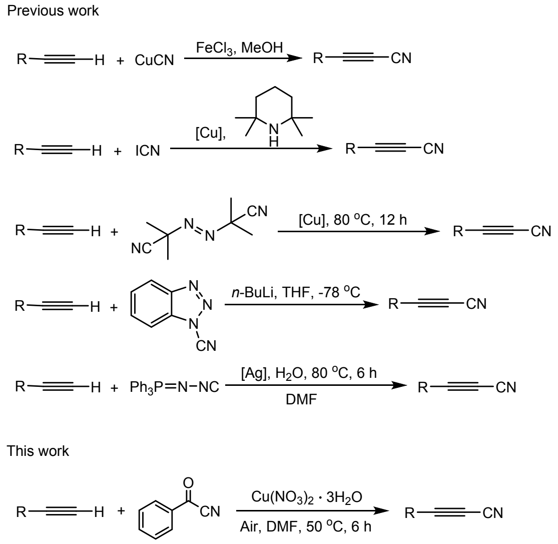
Propiolonitriles are core structural motifs in biologically active molecules. For example, APN-TMPP can be used as a peptide probe [1] and CBTF as a precursor of antibody drug [2] (Fig. 1). Propiolonitriles are also versatile synthons in organic chemistry for the synthesis of various heterocyclic compounds associated with interesting chemical and biological properties [3]. In addition, the important two functionalities of propiolonitriles, alkyne and nitrile, can be served as a versatile building block and easily transformed into various derivatives, such as amides, amidines, amines, and triazoles etc [4]. Although the synthesis of propiolonitriles can start from many substrates [3, 5], the typical methods generally utilize the reactions of terminal alkynes with cyanating agents, which include i) the direct cross coupling between terminal alkynes and CuCN or NaCN [6]; ii) the copper-catalyzed reactions of terminal alkynes with cyanogen iodide [7]; iii) the copper-catalyzed direct cyanation of terminal alkynes using AIBN (azobisisobutyronitrile) as a cyanide source [8]; iv) the electrophilic cyanation of terminal alkynes using 1-cyanobenzotriazole [9]; and v) the silver-catalyzed direct cyanation of terminal alkynes with *N*-isocyanoiminotriphenylphosphorane [10] (Scheme 1). However some methods use strongly toxic cyanating reagents, excess catalysts and harsh reaction conditions. Therefore it is of great importance to explore a mild, safe and simple way to synthesize propiolonitriles.



APN-TMPP (peptide probe) CBTF (precursor of antibody drug)

Fig. 1 Representative examples bearing 3-arylpropiolonitrile

Benzoyl cyanide is a stable and less toxic chemical. It can be easily prepared by the reaction of nontoxic and inexpensive $K_4[Fe(CN)_6]$ with benzoyl chloride according to our investigation [11]. It has been also used for the cyanide source in organic synthesis [12]. Herein, we report an efficient method for copper-catalyzed direct cyanation of terminal alkynes with benzoyl cyanide under mild condition using air as an oxidant.



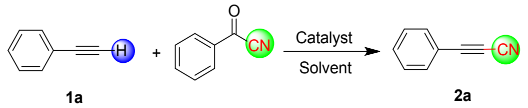
Scheme 1 Preparation of propiolonitriles

∗ Corresponding author. e-mail: lizheng@nwnu.edu.cn

Results and Discussion

Initially the reaction of phenylethyne with benzoyl cyanide was selected as the model reaction to screen the optimal conditions. The different catalysts and solvents at different temperature were investigated. The results are summarized in Table 1. The reaction was first tested in DMF at 50 ºC in the absence of a catalyst, but no product was detected (Table 1, entry 1). The Cu(I) salts such as CuI and CuBr as catalysts were investigated (Table 1, entries 2, 3). To our delight, 3-phenylpropiolonitrile (**2a**) could be obtained in good yield when the reaction was catalyzed by CuI in DMF at 50 ºC for 6 h in open air (Table 1, entry 2). The Cu(II) salts such as Cu(OAc)$_2$, CuSO$_4$, CuCl$_2$ and Cu(NO$_3$)$_2$·3H$_2$O as catalysts exhibited different effects for the reaction (Table 1, entries 4−7). The best yield (79%) was obtained by using Cu(NO$_3$)$_2$·3H$_2$O as a catalyst (Table 1, entry 7). Furthermore, the higher temperatures were also tested, but the reaction yield could not be further improved (Table 1, entries 8, 9). In addition, the other organic solvents were also attempted for the reaction. However, low yield of **2a** was isolated in DMSO and MeCN (Table 1, entries 10, 11), and no product was obtained in MeOH, dioxane, THF and PhMe. The reaction was also tested under nitrogen atmosphere, but no product **2a** was observed (Table 1, entry 12). This result implied that air is an indispensable condition for the reaction.

Table 1 Optimization of the reaction conditions[a]

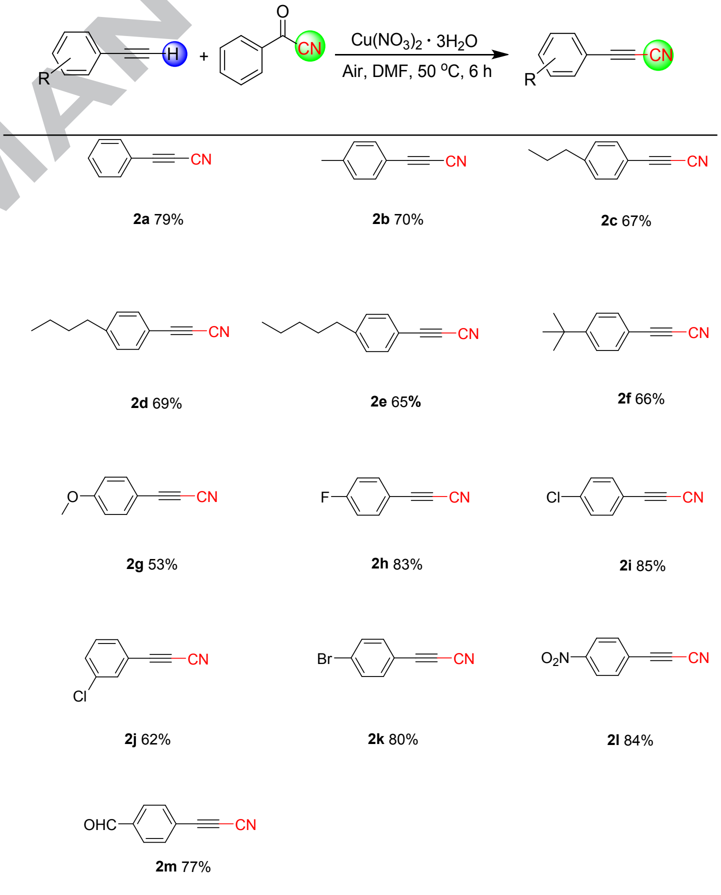


Entry	Catalyst	Solvent	Temperature (ºC)	Yield (%)[b]
1	None	DMF	50	0
2	CuI	DMF	50	64
3	CuBr	DMF	50	Trace
4	Cu(OAc)$_2$	DMF	50	Trace
5	CuSO$_4$	DMF	50	32
6	CuCl$_2$	DMF	50	43
7	Cu(NO$_3$)$_2$·3H$_2$O	DMF	50	79
8	Cu(NO$_3$)$_2$·3H$_2$O	DMF	80	62
9	Cu(NO$_3$)$_2$·3H$_2$O	DMF	120	48
10	Cu(NO$_3$)$_2$·3H$_2$O	DMSO	50	53
11	Cu(NO$_3$)$_2$·3H$_2$O	MeCN	50	25
12[c]	Cu(NO$_3$)$_2$·3H$_2$O	DMF	50	0
13[d]	Cu(NO$_3$)$_2$·3H$_2$O	DMF	50	31
14[e]	Cu(NO$_3$)$_2$·3H$_2$O	DMF	50	62
15[f]	Cu(NO$_3$)$_2$·3H$_2$O	DMF	50	78

[a] Reaction conditions: **1a** (1 mmol), benzoyl cyanide (1 mmol), catalyst (0.2 mmol) in solvent (5 mL) was stirred for 6 h in open air. [b] Isolated yield. [c] Under N$_2$ atmosphere. [d] 0.05 mmol of catalyst was used. [e] 0.1 mmol of catalyst was used. [f] 0.5 mmol of catalyst was used.

By using the optimized conditions, synthesis of 3-arylpropiolonitriles were examined by reactions of terminal alkynes with benzoyl cyanide in DMF under open air condition using Cu(NO$_3$)$_2$·3H$_2$O as a catalyst. The results were summarized in Table 2. It was found that 3-arylethynes containing electron-donating groups, such as 4-substituted Me, *n*-Pr, *n*-Bu, *t*-Bu, Amyl and MeO, on aromatic rings afforded the corresponding products in good yield (**2a-2g**). In contrast, 3-arylethynes bearing electron-withdrawing groups (F, Cl, Br, NO$_2$ and CHO) on their aromatic rings afforded the desired products in high yield (**2h-2m**). These results indicated that electron effect has a certain impact on the yield. Electron-withdrawing effect can increase the nucleophilicity of terminal carbon of alkynes and benefit the attack of CN$^-$ in the reaction. In addition, aliphatic terminal alkynes, such as 1-heptyne and cyclopropylethyne, were also tested for the cyanation with benzoyl cyanide. Unfortunately no any products were observed.

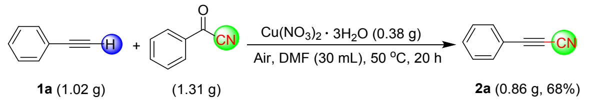
Table 2. Synthesis of 3-arylpropiolonitriles[a]



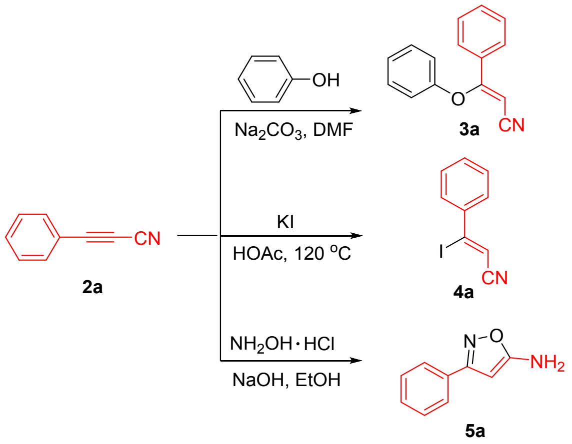
[a] Reaction conditions: arylethyne (1 mmol), benzoyl cyanide (1 mmol), Cu(NO$_3$)$_2$·3H$_2$O (0.2 mmol) in DMF (5 mL) was stirred at 50 ºC for 6 h in open air.

It is worthy to mention that the cyanation of **1a** with benzoyl cyanide to synthesize **2a** could also be performed on gram-scale and give the corresponding product in good yield (Scheme 2). The reaction of 1.02 g of **1a** with 1.31 g of benzoyl cyanide in 30 mL of DMF in the presence of 0.38 g of Cu(NO$_3$)$_2$·3H$_2$O was performed at 50 ºC for 20 h to give **2a** in 68% yield (0.86 g) isolated yield. The success of this gram scale reaction further showed the potency of optimized condition for the bulk processes.

To illustrate the applications of propiolonitriles, some functionalizations of **2a** were implemented (Scheme 3). The reactions of **2a** with phenol, potassium iodide, or hydroxylamine could smoothly synthesize *Z*-3-phenoxy-3-phenylacrylonitrile **3a** [13], *Z*-3-iodo-3-phenylacrylonitrile **4a** [14] and 3-phenylisoxazol-5-amine **5a** [15]. These structures were confirmed by comparison the analytical data with literatures. These products are useful organic synthetic intermediates.

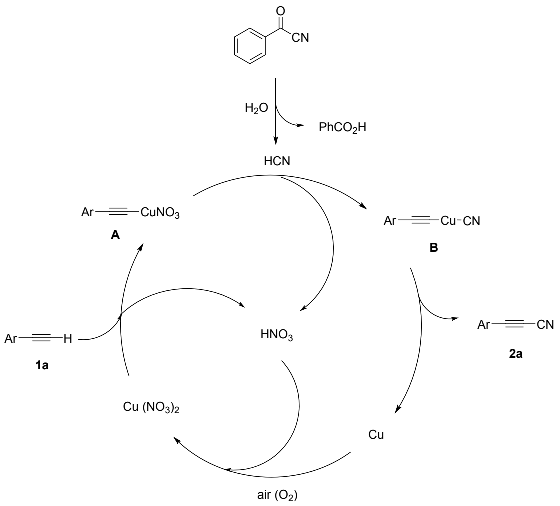


Scheme 2 Gram-scale synthesis of **2a**



Scheme 3 Transformations of propiolonitrile **2a**

On the basis of the above experimental results, a plausible mechanism is proposed for the synthesis of **2a** by reaction of **1a** with benzoyl cyanide (Scheme 4). Initially, the reaction of **1a** with $Cu(NO_3)_2$ forms (phenylethynyl)copper nitrate (**A**) [8]. Meantime, the reaction of benzoyl cyanide with water from $Cu(NO_3)_2.3H_2O$ produces HCN *in situ* [16]. Then the ligands exchange between **A** and HCN gives (phenylethynyl)copper cyanide (**B**) as an intermediate [17]. **B** can easily afford **2a** as a final product by reductive elimination. Meanwhile Cu(0) produced can be readily oxidized by oxygen from air to $Cu(NO_3)_2$ in the presence of HNO_3 produced in the system.



Scheme 4 Proposed mechanism for **2a**.

In summary, copper-catalyzed direct cyanation between terminal alkynes and benzoyl cyanide to form propiolonitrile under mild reaction conditions was developed. The salient features of this protocol include use of less toxic, stable and easy to handle cyanating agent, high yield and mild condition. This method provides an efficient way to prepare propiolonitriles, which are useful intermediates for many important organic chemicals.

Acknowledgements

The authors thank the National Natural Science Foundation of China (21462038) for the financial support of this work.

Appendix A. Supplementary data

Supplementary data to this article can be found online at

References

1. O. Koniev, G. Leriche, M. Nothisen, J. Remy, J. Strub, C. Schaeffer, A.V. Dorsselaer, R. Baati, A. Wagner, Bioconjugate Chem. 25 (2014) 202−206.
2. S. Kolodych, O. Koniev, Z. Baatarkhuu, J. Bonnefoy, F. Debaene, S. Cianférani, V.D. Dorsselaer, A. Wagner, Bioconjugate Chem. 26 (2015) 197−200.
3. P.K. Sharma, S. Ram, N. Chandaka, Adv. Synth. Catal. 358 (2016) 894−899.
4. (a) Z. Rappoport, The Chemistry of the Cyano Group, Interscience Publishers, London, 1970; (b) R.C. Larock, Comprehensive Organic Transformations: A Guide to Functional Group Preparations, VCH, Weinheim, 1989; (c) Z. Cheng, W. Li, F. He, J. Zhou, X. Zhu, Bioorg. Med. Chem. 15 (2007) 1533−1538; (d) N. Heard, J. Turner, J. Org. Chem. 60 (1995) 4302−4304.
5. F. Shu, Q. Zheng, W. Dong, Z. Peng, D. An, Can. J. Chem. 95 (2017) 144−148.
6. (a) Y. Li, D. Shi, P. Zhu, H. Jin, S. Li, F. Mao, W. Shi, Tetrahedron Lett. 56 (2015) 390−392; (b) F.T. Luo, R.T. Wang, Tetrahedron Lett. 34 (1993) 5911−5914; (c) P. Liu, R.J. Clark, L. Zhu, J. Org. Chem. 83 (2018) 5092−5103.
7. K. Okamoto, M. Watanabe, N. Sakata, M. Murai, K. Ohe, Org. Lett. 15 (2013) 5810−5813.
8. G. Rong, J. Mao, Y. Zheng, R. Yao, X. Xu, Chem. Commun. 51 (2015) 13822−13825.
9. T.V. Hughes, M.P. Cava, J. Org. Chem. 64 (1999) 313−315.
10. H. Wang, P. Mi, W. Zhao, R. Kumar, X. Bi, Org. Lett. 19 (2017) 5613−5616.
11. Z. Li, S. Shi, J. Yang, Synlett 15 (2006) 2495−2497.
12. (a) T. Watahiki, S. Ohba, T. Oriyama, Org. Lett. 5 (2003) 2679−2681; (b) A. Baeza, C. Najera, J. M. Sansano, J. M. Saa, Tetrahedron: Asymmetry 16 (2005) 2385−2389; (c) L. Wang, L. Pan, Q. Chen, M. He, Chin. J. Chem. 32 (2014) 1221−1224; (d) H. Song, X. Liu, C. Wang, J. Qiao, W. Chu, Z. Sun, Asian J. Org. Chem. 6 (2017) 1693−1698.
13. W. Zhou, Y. Zhang, P. Li, L. Wang, Org. Biomol. Chem. 10 (2012) 7184−7196.
14. Z. Guan, Z. Liu, W. Shi, H. Chen, Tetrahedron Lett. 58 (2017) 3602−3606.
15. I. Issei, N. Norio, Chem. Pharm. Bull. 14 (1966) 1277−1286.
16. (a) J. Jin, Q. Wen, P. Lu, Y. Wang, Chem. Commun. 48 (2012) 9933−9935; (b) L. Zhang, X. Gu, P. Lu, Y. Wang, Tetrahedron 72 (2016) 2359−2363; (c) D. Xie, Z. Li, Tetrahedron 74 (2018) 1135−1143; (d) X. Hu, H. Li, J. Yang, Z. Li, Synlett 25 (2014) 1786−1790; (e) Z. Li, Y. Ma, J.Xu, J. Shi, H. Cai, Tetrahedron Lett. 51 (2010) 3922−3926.
17. A.B. Pawar, S. Chang, Chem. Commun. 50 (2014) 448−450.

Highlight

- Less toxic, stable and easy to handle cyanating agent
- Air as an oxidant
- Mild condition
- Up to 85% yield