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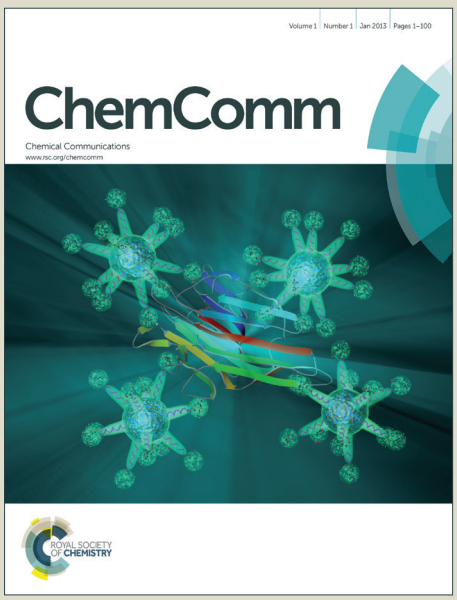

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Cu-Catalyzed direct cyanation of terminal alkynes with AMBN or AIBN as cyanation reagents

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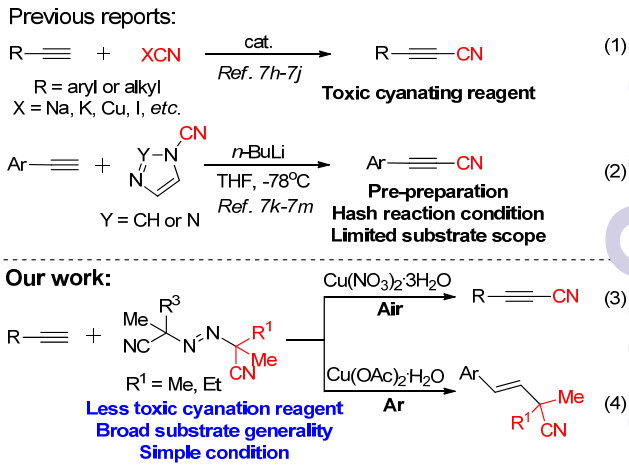
A Cu-catalyzed direct cyanation of terminal alkynes was reported with broad subsrate generality in moderated to high yield, and AMBN (Azobisisoamylonitrile)/AIBN (Azobisisobutyronitrile) are used as less toxic and effective cyanating source in open air. Interestingly, addition products were selectively achieved as major product in same condition under argon.

The nitrile group plays an important role in organic chemistry, which not only served as a key unit in plentiful pharmaceuticals and bioactive compounds[1], but also as a versatile group that can be easily transformed into various derivatives, such as nitrogen-containing heterocycles, amides, amines, etc.[2] In this context, cyanation reaction has been an important research orientation in organic chemistry, including traditional cyanation reactions such as Sandmeyer reaction, which provide effective methods to prepare aromatic nitriles.[3] And various cyanation reagents have been well explored by many researchers in recent decades.[3-5] Convenient methods for the synthesis of aromatic nitriles are the transition metal-catalyzed cyanation of aryl halides like Rosenmund-von Braun reaction.[4a] However, prefunctionalization is required for the substrate and stoichimetric toxic metal cyanation regents are adopted, including MCN(M= Cu, K, Na).[4] Although there are few of new organic cyanation reagents were developed, it costs money or takes steps to prepare them.[5] Therefore, a range of green cyanation regents were discovered. Cheng and co-workers reported a copper-catalyzed cyanation of arylboronic acids, in which safe reagent DDQ was employed as the cyanide source.[5a] In 2012, Wang's group disclosed using benzyl cyanide as an operational benign cyanide surrogate in copper-catalyzed cyanation of 2-phenylpyridines.[5b] Acetonitrile was firstly reported as a cyanide source for palladium-catalyzed cyanation of aryl halide by Cheng and co-workers.[5c] Interestingly, in 2010 Chen's group illustrated that DMF can be employed as the source of "C" atom and aqueous ammonia as the source of "N" atom in their cyanation reaction.[5d] Very recently, Han and co-workers reported a copper-mediated cyanation of 2-phenylpyridines using AIBN as cyanating reagent, which provided a novel protocol for C-H cyanation via a free radical "CN" process.[5e] Inspired by these results, herein, we present a copper-catalyzed cyanation of terminal alkyne with AIBN as cyanation reagent.

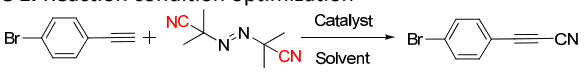
Terminal alkynes are very useful compounds, which are abundant in natural products, and they can be easily manipulated to form other compounds via additions with aryl halides,[6a] amines,[6b] arylboronic acids,[6c] etc.[6d-6g] Besides, the terminal position tend to be served as ideal reaction sites for further introducing the functional group by replacement of the C(*sp*)-H bond. Relevant researches on the functionalization of terminal alkyne were well explored, including methylation,[7a] trifluoromethylation,[7b-7c] halogenation,[7d] cyanation, etc.[7h-7n] For the cyanation reactions metal cyanides proved to be straightforward and effective reagents despite the metal waste and toxicity (Scheme 1, eq 1).[7h-7j] Very recently, Okamoto *et al.* have successfully achieved the cyanation of internal alkynes by using cyanogen iodide as cyanation reagent.[7k] Other non-metal cyanide regents such as 1-cyanoimidazole were reported for the same transformations, while harsh conditions were required (eq 2).[7k-7m] What's more, these kind of cyanation surrogates are not readily available and toxic. Herein, we disclosed a copper-catalyzed cyanation of terminal alkynes under mild conditions with broad substrates generality, more importantly, AMBN or AIBN are used as a less toxic cyanation reagent under air atmosphere (eq 3). And the addition products were observed as major product when the reaction carried out in argon (eq 4).



Scheme 1. Approaches to the cyanation of terminal alkynes.

We initiated our study with 4-bromophenylacetylene **1a** as a model substrate. To our delight, desired product **3a** was obtained in 26% yield when the reaction was treated with AIBN (0.6 mmol) and $Cu(OAc)_2$ (20 mol%) in acetonitrile at 80 °C for 12 hours in air (Table 1, entry 1). No cyanation product was detected at the absence of the copper catalyst. Then a range of copper catalysts were tested, and the yield was increased to 48% by switching $Cu(OAc)_2$ with $Cu(acac)_2$ (entry 9). Other catalysts such as CuCl, $CuBr_2$ and CuI showed inferior results for this transformation (entries 3-8). Cupric nitrate was proved to be the best and afforded **2a** with 70% isolated yield (entry 10). The use of other solvents such as DMSO, DCE and 1,4-dioxane resulted in much lower yields (entries 11-14). In order to improve the reaction yield, AMBN (Azobisisoamylonitrile) was tried as cyanation reagent, which is a derivative of AIBN. It's pleased to find that slightly higher yield 73% was obtained under the same reaction condition (entry 15). Further investigation showed this reaction cannot proceed under argon atmosphere (entry 16), indicating that oxygen is indispensable for this process. However, the yield was not further promoted under oxygen atmosphere (entries 17). It's noteworthy that no self-coupling product of acetylene was generated in this reaction.

Table 1. Reaction condition optimization[a]



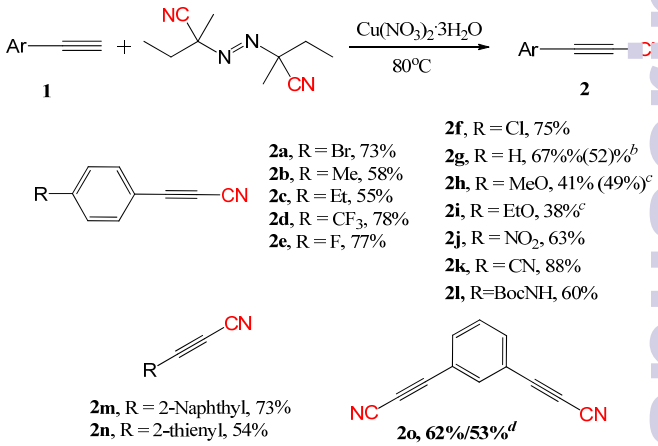
1a 2a

entry	catalyst	solvent	yield (%)[b]
1	$Cu(OAc)_2.H_2O$	CH_3CN	26
2	-	CH_3CN	nd
3	Cu	CH_3CN	27
4	CuCl	CH_3CN	19
5	$CuCl_2 2H_2O$	CH_3CN	30
6	CuBr	CH_3CN	38
7	$CuBr_2$	CH_3CN	28
8	CuI	CH_3CN	29
9	$Cu(acac)_2$	CH_3CN	48
10	$Cu(NO_3)_2 3H_2O$	CH_3CN	70
11	$Cu(NO_3)_2 3H_2O$	DCE	trace
12	$Cu(NO_3)_2 3H_2O$	Dioxane	trace
13	$Cu(NO_3)_2 3H_2O$	Ethanol	18
14	$Cu(NO_3)_2 3H_2O$	DMSO	12
15[c]	$Cu(NO_3)_2 3H_2O$	CH_3CN	73
16[d]	$Cu(NO_3)_2 3H_2O$	CH_3CN	nd
17[e]	$Cu(NO_3)_2 3H_2O$	CH_3CN	59

[a] Reaction condition: 4-Bromophenylacetylene **1a** (0.3 mmol), AIBN (0.6 mmol), catalyst (20 mol%), solvent (4.0 mL), 80 °C, 12 h in open air. [b] Isolated yield; nd: not detected. [c] AMBN (0.6 mmol) instead of AIBN. [d] Under Ar atmosphere. [e] Under oxygen atmosphere.

With optimized reaction condition in hand, we proceeded to investigate the scope generality of this cyanation reactions. A number of arylacetylenes were first examined under the optimized reaction conditions, and the results were summarized in Scheme 2. As expected, a variety of functional groups, including trifluoromethyl, methoxy, halogen and nitro, were well tolerated.

Scheme 2. Substrate scope of arylacetylenes **1** in Cu-catalzyed cyanation [a]

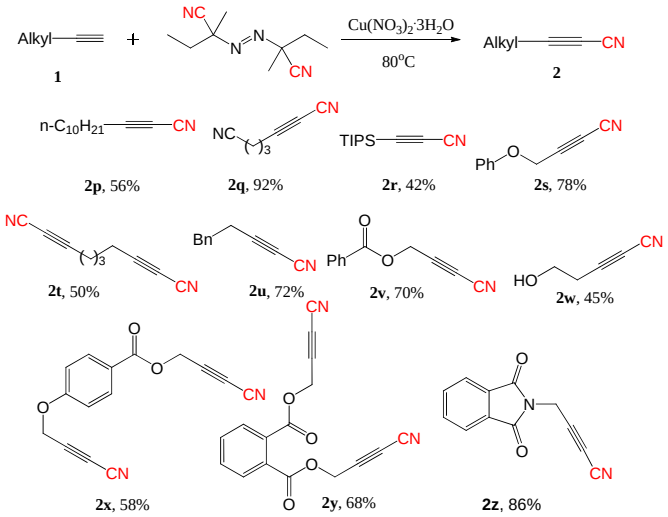


[a] Reaction condition: aryacetylene (0.3 mmol), AMBN (0.6 mmol), $Cu(NO_3)_2 H_2O$ (20 mol%), CH_3CN (4 mL), 80 °C, 12h, air. [b] Rection carried out in 4.0 mmol scale. [c] AIBN (0.6 mmol) instead of AMBN (0.9 mmol).

By comparing the results, it's not difficult to find that substrates bearing electron-withdrawing groups on the benzene rings tend to accomplish the reaction in much higher yields than those with electron-donating analogues. Moderate yield was obtained when phenylacetylene was applied to react with AMBN. Methyl and ethyl substituted substrates afforded the corresponding products (**2b**, **2c**) in slightly lower yields. Due to the strong electron-withdrawing property of trifluoromethyl group, **2d** was afforded in much higher yield compared with **2b**. Notably, Halogen substituted phenylacetylenes also gave the corresponding products in good yields (**2a**, **2e**, **2f**), and the halogen group survived well after reaction which were applicable for further functionalization. It's noteworthy when the reaction was conducted on gram scale by using pheylacetylene (**1g**) as substrate and **2g** was obtained in the yield of 52%. For some substrates (**2h**, **2i**), AIBN shows better efficiency than AMBN. Nitro and cyano groups were well tolerated and the reactions were furnished in good to excellent yields. For 1-naphthyl and 2-thienyl substrates, the cyanation reactions can proceed smoothly and satisfied yields were obtained (**2m**, **2n**). Furthermore, 1,3-diethynylbenzene was also suitable for this reaction, affording **2o** in 62% yield. Interestingly, no single cyanation products were detected in the reaction, which shows the high efficiency of this cyanation protocol. However, 3-ethynylpyridine is not suitable for this reaction, mainly because of the coordination effect between copper catalyst and substrate. Likewise, amino substituted phenylacetylene can not successfully cyanated under standard reaction conditions, unless the amine group was protected as an amide (**2l**).

After the exploration of the reaction scope with aryl alkynes, we next turned our attention to the aliphatic alkynes (Scheme 3). To our delight, 56% yield of **2p** was isolated when 1-dodecyne was performed under standard condition with AMBN. Encouraged by this result, we next tried various alkylacetylenes. Obviously, the substrate with cyan group gave high yield (**2q**, 92%). Silylacetylene

Scheme 3. Cyanation with various alkylacetylene[a]



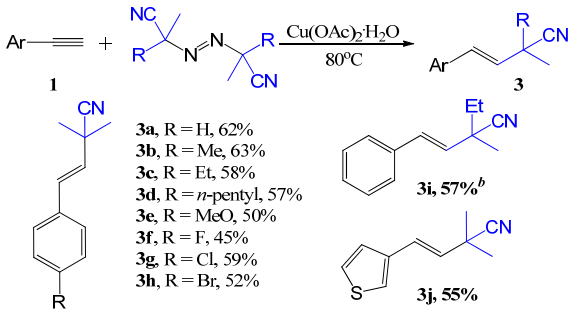
[a] Reaction condition: Aliphatic alkyne **1** (0.3 mmol), AMBN (0.6 mmol), $Cu(NO_3)_2{\cdot}3H_2O$ (20 mol%), CH_3CN (4.0 mL), 80 °C, 12 h, air.

was also compatible by our method, giving **2r** in the yield of 42%. Good yields were obtained when substrates **1s** and **1v** were tested, which provides an efficient strategy to introduce cyan group to specific molecules containing ether or ester groups. It's encouraging to see that **1w** was also suitable for this reaction which contains an free hydroxyl group, although moderate yield was obtained. It's quite excited to find out that diynes also react smoothly under this condition (**1t**, **1y**). Even unsymmetrical diyne (**1x**) can be tolerated by the reaction and afford the desired product in good yield. Moreover, alkyne **1z** which contains an amide group was suitable for this reaction, giving **2z** in 86% isolated yield.

During the reaction optimization, 28% of compound **3h** was obtained when the reaction was conducted under argon atmosphere with cupric acetate as catalyst. Literature investigation found out that such vinyl isobutyronitrile compounds are except as the byproducts in some reactions.[8a-8b] Besides, Onaka's group developed a method to access this vinyl isobutyronitrile from unsaturated alcohols with TMSCN.[8c] However, this strategy suffers the drawback of using expensive catalyst and combined with limited substrates generality. Therefore, preparing vinyl isobutyronitriles from commercial available starting materials with exclusive *E* isomers seems to be very attractive. After optimization (Table S1),[9] we found that excess amount of alkynes should be used due to the self-coupling byproducts were inevitably generated under this condition. Generally, moderate yields were obtained when arylacetylenes were employed to react with AIBN in pyridine with cupric nitrate as catalyst at 80 °C under argon atmosphere for 12 hours (Scheme 4). Obviously this reaction was little influenced by the electron nature of the substrates, as both 4-fluoro and 4-methoxyl phenylacetylenes provided the products in moderate yields. However, aliphatic acetylene was not tolerated for this reaction, and no conversion of the substrate was detected.

According to the reported literatures and our observations (Scheme S1),[9] a plausible mechanism was proposed to rationalize the formation of both **2** and **3** (Scheme 6). Firstly, the process was

Scheme 4. Reaction scope of preparation the vinyl isobutyronitriles[a]

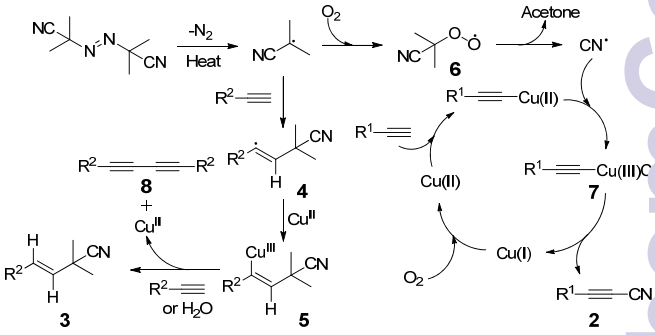


[a] Reaction condition: Arylacetylene (0.6 mmol), AIBN (0.15 mmol), $Cu(OAc)_2{\cdot}H_2O$ (20 mol%), pyridine (4 mL), 80 °C, 12h, Ar; yields were based on limiting reagent of AIBN or AMBN. [b] AMBN (0.15 mmol) instead of AMBN.

initiated via the generating of an isobutyronitrile radical from AIBN by heating,[6] which then reacted with arylacetylene to generate **4** in argon atmosphere. The radical process was confirmed by control reaction in the precence of TEMPO, in which the reaction was inhibited obviously (Scheme S1, eq 3).[9] Intermediate **4** then reacted with Cu^{II} species to yield vinyl copper(III) complexes **5**. Finally, intermediate **5** went through a protonation process by trapping proton from arylacetylene, or partly from H_2O in the system, to produce desired product **3** and regenerated Cu(II) catalyst.[10] And this proton trasfer procee was confirmed by observation a certain amount of coupling pyprodcut,[8] which was not detected under the same condition in the absence of AIBN, and the deuterium labeling experiment.[9]

When the reaction was conducted in air, the initially generated isobutyronitrile radical was then oxidized to radical **6** by O_2. After releasing one equivalent of acetone, radical **6** converted to the cyano radical;[5f] and the (phenylethynyl)copper could be a very possible intermediate in this reaction to trap the cyano radical to give **7** through single-electron transfer,[5g] since moderate yield was obtained for the same product when (phenylethynyl)copper was used as the srarting materal instead of alkyene (Scheme S1, eq 5).[9] Finally, reductive elimination of intermediate **7** delivered the product **2** and Cu(I).[11] The Cu(I) was next oxidized to Cu(II) by O_2 and went back to the reaction cycle.

In summary, we have developed an efficient copper catalyzed cyanation of terminal alkynes with AMBN/AIBN as effective



Scheme 6. Plausible reaction pathways.

cyanating source. Various alkynes were tolerated with this protocol, including not only aryl, alkyl or silyl substituted alkynes, but also their ether, ester and amide derivatives. Interestingly, vinyl isobutyronitrile products were selectively achieved from the same starting materials by simply altering the reaction condition under inert gas atmosphere. Comparing with previous reports on the synthesis of cyanoacetylenes, our method has the remarkable advantages in less toxic cyanating reagent and wide substrate scope. But drawbacks are still exist such as excess amout of alkynes were used in the systhesis of vinyl isobutyronitrile compounds. Further studies on the cyanating reactions with AIBN/AMBN as cyanating reagent are ongoing in our group.

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