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Cu(II)-Catalyzed Synthesis of Naphthalene-1,3-diamine Derivatives from Haloalkynes and Amines

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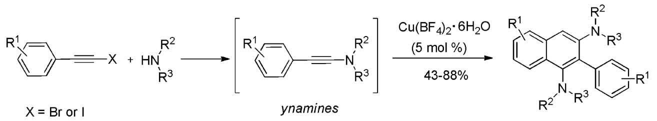
ABSTRACT



An efficient procedure for the preparation of naphthalene-1,3-diamine derivatives by copper-catalyzed haloalkynes with amines has been reported. The reaction was supposed to proceed through a coupling reaction followed by the dimerization of ynamines.

Transition-metal-catalyzed reactions are vital tools for constructing carbon–carbon and carbon–heteroatom bonds in organic synthesis, and substantial advances have been made during the past decades.[1] In particular, copper catalyst systems have been widely applied as a powerful tool in various synthetic areas, such as for the preparation of heterocyclic compounds, natural products, pharmaceuticals, and molecular organic materials.[2] The field of ynamide chemistry has experienced rapid development in the past decade;[3] particularly, copper-catalyzed reactions for the preparation of ynamides have provided efficient, straightforward, and reliable access to useful building blocks.[4] On the contrary, although ynamine chemistry has a long history,[5] the high reactivity caused much difficulty in the experimental preparation and general handling of ynamines and rendered ynamine chemistry inaccessible.[6] Hence it is a challenge to develop new methods for preparation and application of ynamines.

Haloalkynes are useful intermediates and versatile building blocks.[7] Several mild and convenient methods have been developed and thus have increased the attractiveness of this

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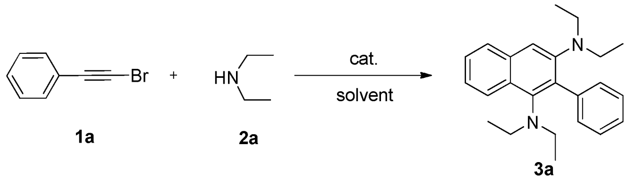
class of compounds in organic synthesis.[8,9] Recently, our group has reported transition-metal-catalyzed bond formation reactions, nucleophilic additions, and homocoupling reactions of haloalkynes.[10] As part of our continuing project in the functionalization of haloalkynes, here we wish to report the first copper-catalyzed one-pot domino synthesis of naphthalene derivatives from haloalkynes and amines. The ynamine was considered to be the intermediate in this transformation process. It is important to note that, very recently, Skrydstrup's group reported an unprecedented dimerization reaction of ynamides in the presence of gold(I) catalysis.[11] The aryl-substituted ynamides could be transformed into a mixture of three kinds of products, and the naphthalene derivatives were one of the products. Therefore, the development of new strategies for constructing naphthalene derivatives with expedient conditions and high efficiency remains an extremely attractive task for organic chemists.

The reaction of phenylethynyl bromide (**1a**) with diethylamine (**2a**, 1 mL) was chosen as the model reaction. First, four different commonly used metal salts were used as the catalyst to conduct this reaction. We found that CuI could afford the naphthalene-1,3-diamine in 36% yield (Table 1, entry 4). The reaction did not proceed without copper salt (Table 1, entry 5). Different copper species were also tested. $Cu(OAc)_2$, CuO, $CuBr_2$, and $Cu(CF_3SO_3)_2$ were also less effective (Table 1, entries 6–9). To our delight, $Cu(BF_4)_2 \cdot 6H_2O$ was superior to any other copper catalyst so far tested and could afford the desired product with 88% isolated yield, and the side product was mainly the 1,3-diyne from the homocoupling of phenylethynyl bromide with 10% isolated yield (Table 1, entry 10). Only trace product was detected using KBF_4 as the catalyst instead (Table 1, entry 11). Then $Cu(BF_4)_2 \cdot 6H_2O$ was used as the catalyst of choice. The reaction showed a strong solvent dependence. Except for the corresponding amine, other organic solvent and water were proven to be inappropriate for the reaction (Table 1, entries 12–16). The lower temperature disfavored the reaction (Table 1, entry 17). After some attempts, we considered that the optimized reaction conditions are as follows: **1a** (1 mmol) with amine (1 mL) and $Cu(BF_4)_2 \cdot 6H_2O$ (5 mol %) at 80 °C for 6 h (Table 1, entry 10).

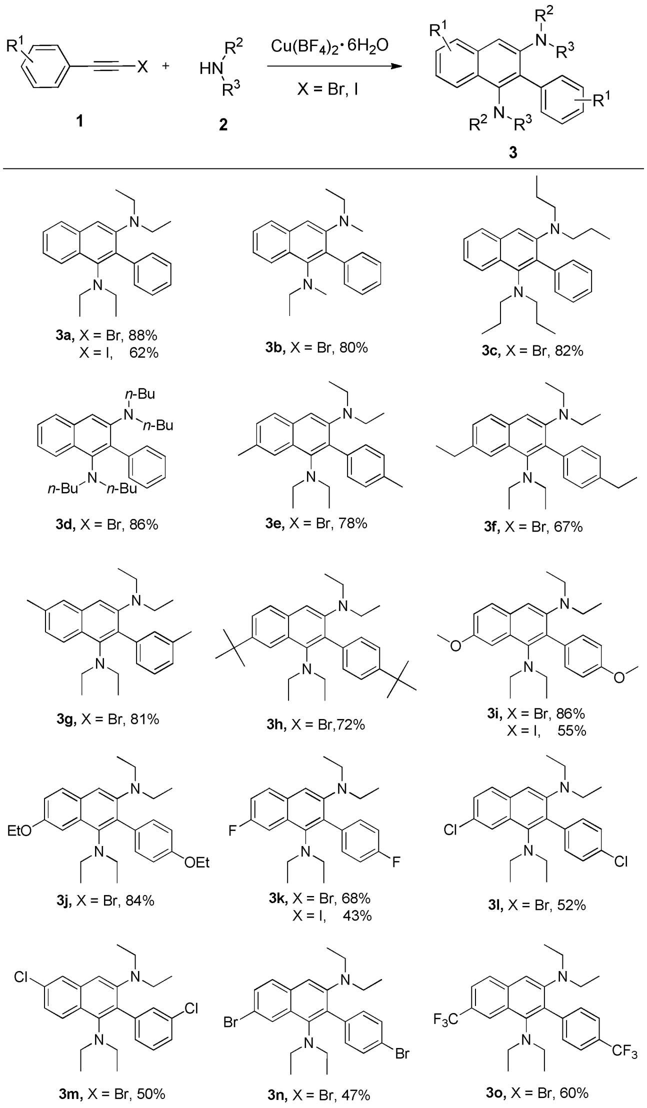
Table 1. Optimization of Reaction Conditions for the Synthesis of Naphthalene-1,3-diamine[a]



entry	catalyst	solvent	yield[b] (%)
1	$Pd(OAc)_2$	$NHEt_2$	np
2	$AgBF_4$	$NHEt_2$	np
3	$FeCl_3$	$NHEt_2$	np
4	CuI	$NHEt_2$	36
5[c]		$NHEt_2$	np
6	$Cu(OAc)_2$	$NHEt_2$	51
7	CuO	$NHEt_2$	40
8	$CuBr_2$	$NHEt_2$	20
9	$Cu(CF_3SO_3)_2$	$NHEt_2$	46
10	$\mathbf{Cu(BF_4)_2 \cdot 6H_2O}$	$\mathbf{NHEt_2}$	**88**
11	KBF_4	$NHEt_2$	trace
12[d]	$Cu(BF_4)_2 \cdot 6H_2O$	CH_3CN	43
13	$Cu(BF_4)_2 \cdot 6H_2O$	DMF	13
14	$Cu(BF_4)_2 \cdot 6H_2O$	toluene	52
15	$Cu(BF_4)_2 \cdot 6H_2O$	DMSO	27
16	$Cu(BF_4)_2 \cdot 6H_2O$	water	trace
17[e]	$Cu(BF_4)_2 \cdot 6H_2O$	$NHEt_2$	45

[a] Reaction conditions: phenylethynyl bromide (1.0 mmol), solvent (1.0 mL), and catalyst (5 mol %) at 80 °C for 6 h. [b] Isolated yield. [c] Without catalysis. [d] Reactions were reacted with other organic solvent or water (1.0 mL) and diethylamine (3.0 mmol) in entries 12–16. [e] Room temperature.

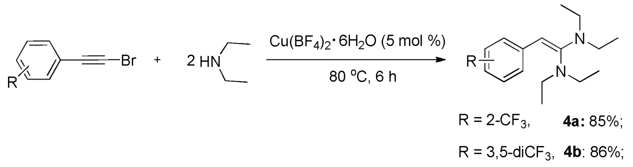
Scheme 1. Copper-Catalyzed Synthesis of Naphthalene-1,3-diamine Derivatives[a]



[a] Reaction conditions: haloalkyne (1.0 mmol), the corresponding amine (1.0 mL), and $Cu(BF_4)_2 \cdot 6H_2O$ (5 mol %) at 80 °C for 6 h. Isolated yields.

With the success in finding the optimum reaction conditions (Table 1, entry 10), the scope and the utility of this method with other haloalkynes and amines under the standard conditions were then investigated in detail. As summarized in Scheme 1, aromatic alkynyl bromides or iodides with either an electron-donating or electron-withdrawing group on the benzene ring were able to generate the corresponding products in moderate to good yields, and alkynyl bromides gave naphthalene-1,3-diamine derivatives in better yields as compared to the corresponding alkynyl iodides (**3a**–**o**). Clearly, the electronic effect plays an important role, as electron-rich substituents on the benzene ring favored the transformation. The reaction conditions were compatible with alkyl, alkyloxy, fluoro, chloro, bromo, and trifluoromethyl groups (**3e**–**o**). It is noteworthy that the aryl bromides and chlorides could further realize varieties of transformations under transition-metal-catalyzed conditions (**3l**, **3m**, and **3n**). Interestingly, for the meta-substituted aromatic 1-bromoalkynes, the reaction could afford the corresponding products regiospecifically (**3g** and **3m**). Unfortunately, substitution at the ortho-position of the aromatic ring was ineffective in the reaction conditions. On the other hand, the structure of the amine was important for the reaction. The alkyl-substituted secondary amines could afford the corresponding products successfully.

Scheme 2. Formation of 2-Substituted 1,1-Ethenediamine Derivatives



Subsequently, 2-trifluoromethyl- and 3,5-bis(trifluoromethyl)-substituted phenylethynyl bromides were reacted under the standard conditions (Scheme 2). However, we were surprised that the 2-substituted 1,1-ethenediamine derivatives were formed in good yields instead of naphthalene-1,3-diamine derivatives. 1,1-Enediamines, also called ketene *N*,*N*-acetals or ketene aminals, are useful intermediates in organic synthesis.[12] However, their exceptional reactivity renders their preparation, storage, and handling difficult, which accounts for how seldom they have been investigated in organic synthesis. Here, the CF_3 on the benzene ring contributed to the delocalization of the pairs on the double bond and strengthened the stability of ynamine intermediates and ketene aminal products.

In summary, we have described the first example of copper-catalyzed synthesis of naphthalene-1,3-diamine derivatives. This reaction appears to involve two consecutive processes, the formation of ynamines from haloalkynes with amines and the dimerization of ynamines. The mild reaction conditions, simple substrate preparation, and one-pot operation of this procedure are attractive aspects for organic synthesis. Although some disadvantages exist in the transformation, such as limited scope and use of a large excess of amine, the reaction is an important application of haloalkynes and paves a way for the development of ynamine chemistry. Further studies on this new process are currently underway in our laboratory.

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Supporting Information Available. Typical experimental procedure and characterization for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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The authors declare no competing financial interest.