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Copper-catalyzed coupling of 1,2-dibromo-1-styrenes with sulfonamides for the preparation of ynamides

Yuan Yang, Xiaoyun Zhang, Yun Liang *

Key Laboratory of Chemical Biology and Traditional Chinese Medicine Research, Ministry of Education, Key Laboratory of Resource Fine-Processing and Advanced Materials of Hunan Province, Hunan Normal University, Changsha, Hunan 410081, China

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ABSTRACT

Ynamides were prepared through an efficient copper-catalyzed coupling reaction. In the presence of copper iodide, 1,10-phenanthroline, and Cs_2CO_3, the coupling reaction of 1,2-dibromo-1-styrenes with sulfonamides proceeded smoothly and generated the corresponding products with excellent isolated yields.

As a result of excellent reactivity of ynamide in the aspect of addition reactions, cycloadditions, cycloisomerization reactions, metal-catalyzed cross-coupling reaction, reduction reaction, oxidation reaction etc., ynamides have become useful synthons in organic synthesis.[1,2] These useful transformations could be utilized to synthesize a variety of nitrogen-containing molecules. Thus, many useful methods have been developed.[3–11] Traditional approaches are focused on (1) the isomerization of propargyl amide,[4] (2) the elimination of halo-substituted enamides,[5] (3) the coupling reaction of alkynyliodonium salts with lithiated amine.[6] Due to the required harsh reaction conditions and poor substrate scope, the synthetic application of these approaches often lack generality. At present, the copper-catalyzed coupling of alkynyl bromides with amides to synthesize ynamides is the most widely applied method.[7] However, this method is also limited to a certain extent because of instability of alkynyl bromides. In order to overcome these limitations (such as harsh reaction conditions, poor substrate scope, and difficulty of preparation of the starting substrate), some new synthetic methods of ynamides are developed. For example, Stahl and co-workers developed a copper-catalyzed method for aerobic oxidative coupling of terminal alkynes with a variety of nitrogen nucleophiles.[8] Jiao and Jia reported a novel Cu-catalyzed aerobic oxidative amidation of propiolic acids to synthesize ynamides via decarboxylation under air.[9] Evano and co-workers used potassium alkynyltrifluoroborates[10a] and alkynylcopper[10b] as alkynylation reagents to prepare ynamides. Besides, Evano and co-workers reported a more general copper-mediated synthesis of ynamide derivatives starting from readily available 1,1-dibromo-1-alkenes.[11] Similar to the 1,1-dibromo-1-alkenes, 1,2-dibromo-1-alkenes are possible alkynylation reagents too. Ranu et al. reported a facile synthesis of (*E*)-2-alkene-4-ynoate system by the coupling of 1,2-diiodo-1-alkenes with acrylic ester.[12] Banerjee et al. also reported a similar result.[13] Our group developed an approach for the highly selective synthesis of unsymmetrical buta-1,3-diynes using 1,2-diiodo-1-alkenes as starting substrate.[14] In this reaction, dehydroiodination of the starting 1,2-diiodo-1-alkenes would generate alkynyl iodines as intermediate and subsequent coupling with acrylic ester or terminal alkyne to form corresponding alkynylation products. Thus, we envisioned that 1,2-dibromo-1-alkenes would be an efficient precursor of alkynyl bromides which could be used to synthesize ynamides by coupling with amides (Scheme 1). In addition, 1,2-dibromo-1-alkenes are more inexpensive and more stable than the common alkynylation reagent of alkynyl bromides.[15] Herein, we reported the first example of the preparation of ynamides from readily available 1,2-dibromo-1-alkenes.

Initially, the coupling reaction of (1,2-dibromovinyl)benzene (**1a**) with *N*-benzyl-tosylamine was selected for optimization of reaction conditions, and the results are summarized in Table 1. Our investigation started by an attempted amination of substrate **1a** with **2a** in THF at 80 °C in the presence of CuI as catalyst, and the desired product **3a** could be isolated in 35% yields (entry 1). This result encouraged us to develop an efficient catalytic system to synthesize ynamides using (1,2-dibromovinyl)benzene as a starting substrate. A variety of *N*,*N*-bidentate ligands, such as 1,10-phenanthroline (1,10-phen), *N*,*N*′-dimethylethanediamine

* Corresponding author. Tel.: +86 10 8887 2576; fax: +86 10 8887 2531.
E-mail address: liangyun1972@126.com (Y. Liang).

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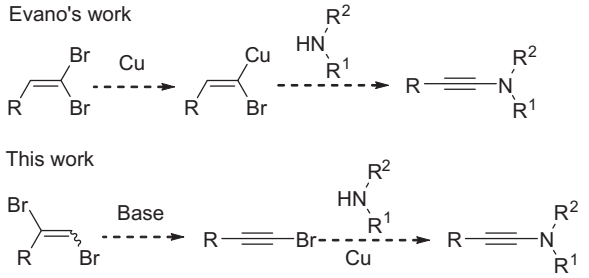
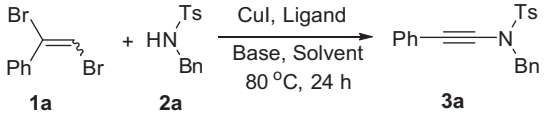


Scheme 1. Synthesis of ynamides by copper-catalyzed coupling of 1,1-dibromo-1-alkenes or 1,2-dibromo-1-alkenes with nitrogen nucleophiles.

Table 1
Optimization of reaction conditions[a]



1a **2a** **3a**

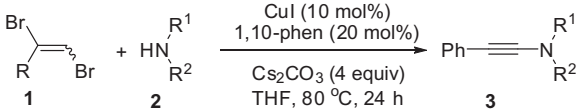
Entry	Ligand	Base	Solvent	Yield of **3a**[b] (%)
1	—	Cs_2CO_3	THF	35
2	1,10-Phen	Cs_2CO_3	THF	96
3	DMEDA	Cs_2CO_3	THF	93
4	Cyclohexane-1,2-diamine	Cs_2CO_3	THF	81
5	2,2′-Bipyridine	Cs_2CO_3	THF	23
6	TMEDA	Cs_2CO_3	THF	20
7	1,10-Phen	NaO*t*-Bu	THF	90
8	1,10-Phen	K_2CO_3	THF	40
9	1,10-Phen	K_3PO_4	THF	43
10	1,10-Phen	Cs_2CO_3	Toluene	82
11	1,10-Phen	Cs_2CO_3	Dioxane	86
12	1,10-Phen	Cs_2CO_3	DMF	71
13[c]	1,10-Phen	Cs_2CO_3	THF	84
14[d]	1,10-Phen	Cs_2CO_3	THF	88
15[e]	1,10-Phen	Cs_2CO_3	THF	99
16[f]	1,10-Phen	Cs_2CO_3	THF	84

[a] Reaction conditions: **1a** (0.39 mmol), **2a** (0.3 mmol), CuI (20 mol %), ligand (40 mol %), base (1.2 mmol), solvent (2 mL), 80 °C, under N_2 atmosphere for 24 h.
[b] Isolated yields.
[c] 100 °C.
[d] 60 °C.
[e] CuI (10 mol %), ligand (20 mol %).
[f] CuI (5 mol %), ligand (10 mol %).

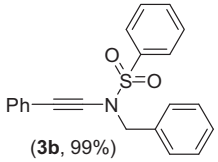
(DMEDA), cyclohexane-1,2-diamine, 2,2′-bipyridine, and *N*,*N*,*N*′,*N*′-tetramethylethylenediamine (TMEDA) were screened. Results indicated that the ligand (1,10-phen) is the best for this coupling reaction (entries 2–6). Subsequently, the effects of base (including Cs_2CO_3, NaO*t*-Bu, K_2CO_3, and K_3PO_4) (entries 7–9) and solvent (including THF, toluene, dioxane, and DMF) (entries 10–12) were examined. Cs_2CO_3 was found to give the best result and THF was found to be the best solvent for the reaction. Finally, the amount of catalyst and the reaction temperature were evaluated. Relatively low yields were found when the reaction was carried out in 60 or 100 °C (entries 13 and 14), and the yield of **3a** was the highest when using 10 mol % loading of CuI and 20 mol % of 1,10-phen (entry 15). Thus, the optimized reaction conditions were as follows: **1a** (0.39 mmol), **2a** (0.3 mmol), CuI (10 mol %), 1,10-phen (20 mol %), Cs_2CO_3 (1.2 mmol), in THF (2 mL) at 80 °C.

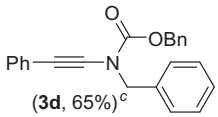
With the standard reaction conditions in hand, the coupling reaction of 1,2-dibromo-1-styrenes with various nitrogen nucleophiles were investigated, and the results are summarized in Table 2. First, we found arylsulfonamides were better nitrogen nucleophiles than carbamates in the coupling reaction with 1,2-dibromovinyl)benzene (**3a**–**e**). Then, we examined the scope of the coupling reaction of (1,2-dibromovinyl)benzene with various tosylamines. As expected, *N*-benzyl substituted tosylamine bearing electron-withdrawing groups such as F or Cl (**3f**,**3g**) or electron-donating group such as OMe (**3h**,**3i**) afforded the corresponding ynamides in perfect yields. Interestingly, *N*-(2-bromobenzyl)-4-methylbenzenesulfonamide could selectively react with (1,2-dibromovinyl) benzene to gain **3j** in 87% yield and no competitive amination or reduction was observed. In addition, 2-furfuryl and phenemyl substituted tosylamines both work well and afforded the corresponding ynamides (**3l**,**3m**) in 90% yield. Under the standard reaction conditions, *N*-alkyl substituted *N*-(phenylethynyl) tosylamine including cycloalkyl (**3n**) and linear-chain (**3o**–**q**) groups could all be obtained in high yields. However, *N*-aryl substituted tosylamines were not suitable substrates for such reaction to form ynamide under the reaction conditions. In this case, tosylamines remained. Meanwhile, the scope and reactivity of 1,2-dibromo-1-styrenes were also examined under the optimized conditions. The benzene ring of 1,2-dibromo-1-styrene bearing either electron-withdrawing groups such as F (**1b**) or electron-donating groups such as Me (**1c**) or OMe (**1d**) gave the corresponding ynamides in high to perfect isolated yields. Unfortunately, aliphatic 1,2-dibromo-1-decene and 1,2-dibromo-1-hexene only afforded corresponding 29% of **3u** and 25% of **3v**.

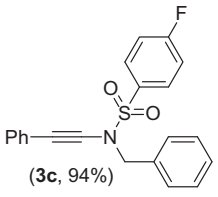
Table 2
Copper-catalyzed coupling of 1,2-dibromo-1-styrenes with nitrogen nucleophiles[a,b]

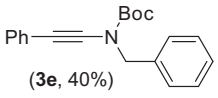


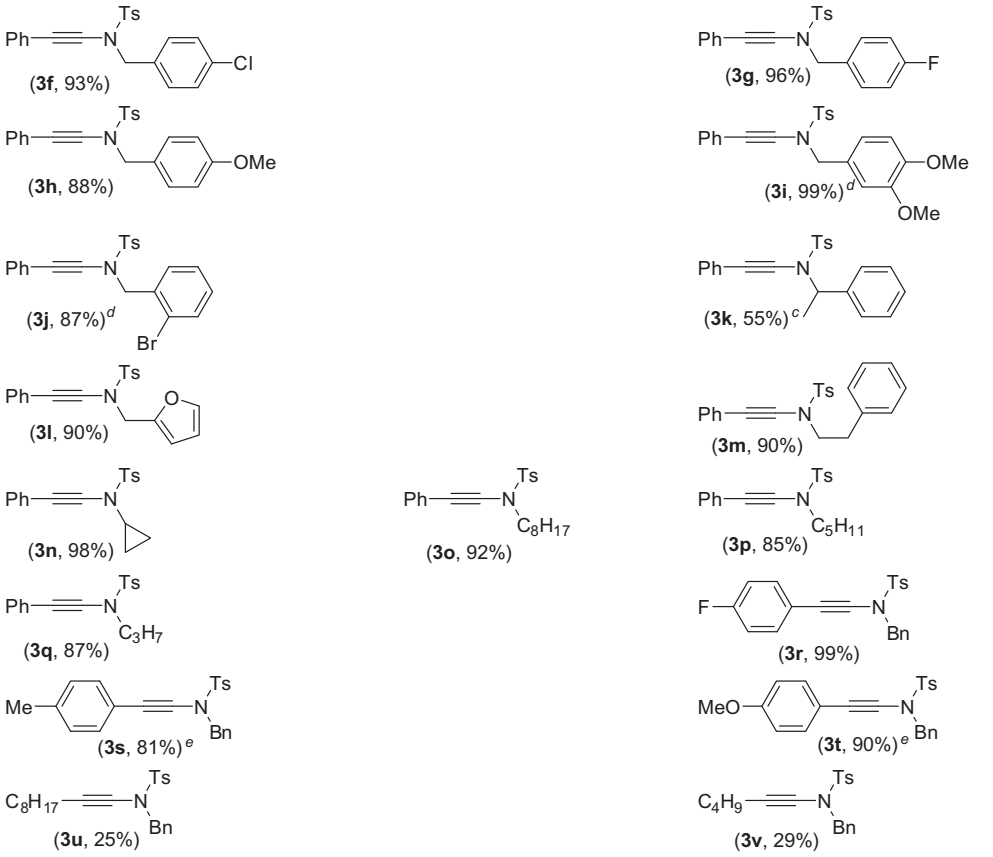
1 **2** **3**


(**3b**, 99%)


(**3d**, 65%)[c]


(**3c**, 94%)

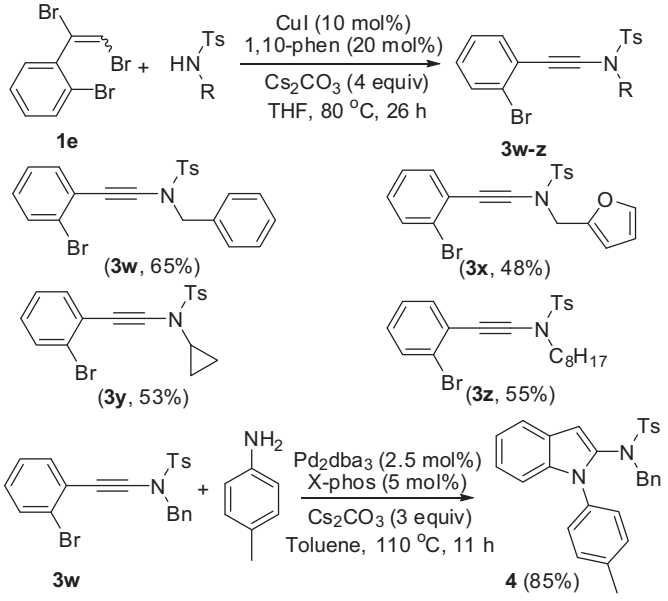

(**3e**, 40%)



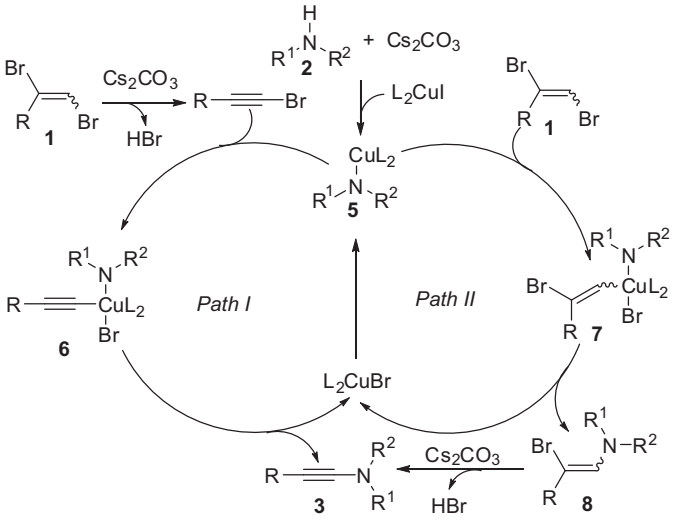
[a] Reaction conditions: **1** (0.39 mmol), **2** (0.3 mmol), CuI (10 mol %), 1,10-phenanthroline (20 mol %), Cs_2CO_3 (1.2 mmol), THF (2 mL), 80 °C, under N_2 atmosphere for 24 h.
[b] Isolated yields.
[c] 35 h.
[d] 27 h.
[e] 28 h.

Importantly, a selective amidative cross-coupling of *ortho*-bromo-2-(1,2-dibromovinyl)benzene could be readily established as shown in Scheme 2. By employing 10 mol % of CuI and 20 mol % of 1,10-phenanthroline, ynamide **3w** was attained in 65% yields. Then, the tandem amination-5-*endo*-dig cyclization of as-prepared *o*-bromoaryl-substituted ynamide **3w** was tested, which is particularly useful in the synthesis of 2-sulfonamido-indoles.[16] One example is the tandem cyclization catalyzed by 2.5 mol % Pd_2dba_3 and 5 mol % X-phos to form 2-sulfonamido-indole **4** in a good yield of 85% (Scheme 2). Reactions of this type could have been used in the synthesis of 2-sulfonamido-indoles with unique structures.

Two experiments were carried out to investigate the reaction mechanism. (1) Phenylethynyl bromide was probed from crude reaction mixtures of the coupling reaction of (1,2-dibromovinyl) benzene (**1a**) with *N*-benzyl-tosylamine (**2a**) by using GC–MS analysis; (2) in the absence of amide **2**, phenylethynyl bromide was also obviously detected by using GC–MS analysis. Based on the present experimental results and the previous reported mechanism,[3–17] a proposed catalytic cycle for the formation of ynamides **3** from **1** and **2** is given in Scheme 3. First, dehydrobromination of the starting 1,2-dibromo-1-alkenes would generate intermediate alkynyl bromides.[12–14] Next, oxidative addition of **5** to the alkynyl bromides presumably generates a copper(III) intermediate **6**. Finally, reductive elimination of **6** would furnish the desired ynamide and regenerate the active Cu(I) species for the catalytic cycle (Path I).[17] According to Evano's work,[11] another mechanism involving the formation of β-bromoenamide by amination of the starting 1,2-dibromo-1-alkenes and its subsequent dehydrobromination to form ynamides could also account for the formation of ynamides from 1,2-dibromo-1-alkenes. Since all attempts to evidence the



Scheme 2. Synthesis of 2-sulfonamido-indole **4**.



Scheme 3. Proposed reaction pathway for the synthesis of ynamides from 1,2-dibromo-1-alkenes.

formation of bromoenamides from crude reaction mixtures failed, this hypothesis was possibly ruled out (Path II).

In summary, the first copper-catalyzed selective synthesis of ynamides from the starting 1,2-dibromo-1-alkenes was developed. In this reaction, dehydrobromination of the starting 1,2-dibromo-1-alkenes would generate intermediate alkynyl bromides and then couple with nitrogen nucleophiles to form ynamides. Further studies on the applications of this method and the coupling reaction with other nucleophiles are underway.

Acknowledgments

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Supplementary data

Supplementary data (experimental procedures and characterization data for all new compounds and copies of NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2012.09.092.

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