Synthetic Methods

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Copper-Mediated Coupling of 1,1-Dibromo-1-alkenes with Nitrogen Nucleophiles: A General Method for the Synthesis of Ynamides**

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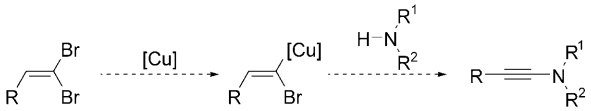
As a result of their superior thermal stability compared to ynamines, ynamides have received considerable attention over the past decade and are clearly emerging as key and versatile synthetic intermediates.[1] Only recently ynamides have been shown to be excellent substrates for ring-closing metathesis,[2] palladium-mediated coupling reactions or rearrangements,[3] cycloisomerization reactions[4] and [2+2] cycloadditions,[5] radical transformations,[6] Pauson–Khand cyclization,[7] diastereoselective sigmatropic rearrangements,[8] yne-carbonyl metathesis,[9] carbometalations,[10] as well as many other useful transformations. They have also been used as efficient synthons for the preparation of a wide array of molecules such as keto-imides,[11] amino-indoles,[12] oxazolones,[13] carbazoles,[14] triazoles,[15] and benzofurans.[16]

In addition to a number of traditional approaches that often lack generality,[1] two methods for the synthesis of ynamides have recently emerged. The first one relies on the use of hypervalent alkynyliodonium salts[4b,7] while the second one, perhaps the most widely applicable to date, is the copper-catalyzed coupling of alkynyl bromides with amides,[17] a modern variant of the Goldberg reaction which has recently been extended to the use of terminal alkynes.[18] Despite these advances, general methods are still needed for the preparation of ynamides, particularly because existing procedures suffer either from limited substrate scope, require the formation of the alkynylating agent, or use a large excess of the amide. An attractive alternative for the preparation of ynamides would rely on the generation of sp^2 carbenoid intermediates starting from readily available 1,1-dibromo-1-alkenes and their further reaction with nitrogen nucleophiles (Scheme 1). If successful, this procedure would be especially convenient and straightforward for the preparation of ynamides.

Drawing from recent experiences in the field of copper-catalyzed cross coupling reactions,[19,20] we wondered whether such a reaction could be performed using catalytic amounts of copper(I) salts. Two important precedents provided a basis for our investigation of this transformation: the synthesis of alkynylphosphonates[21] and internal alkynes[22] by palladium-catalyzed cross-coupling reactions from 1,1-dibromo-1-alkenes. However, several recent examples of metal-catalyzed reactions of vinyl dibromides with nitrogen nucleophiles demonstrated that products resulting from either a regioselective monocoupling[23] or double coupling were obtained in all cases.[24] Even so, we felt that the use of appropriate reaction conditions would allow us to realize a mild and general procedure for the synthesis of ynamide derivatives. To our delight, we found that copper catalysis functions well in this context, and herein we report the first examples of the synthesis of ynamides from 1,1-dibromo-1-alkenes.



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

We initiated our studies by examining the reaction of pyrrolidin-2-one (**1**) with a slight excess of (2,2-dibromovinyl)benzene (**2**; 1.5 equiv) in the presence of catalytic amounts of copper(I) iodide and *N*,*N*′-dimethylethylenediamine (Figure 1).[25] The reaction turned out to be heavily dependent on the reaction conditions. The choice of base was especially critical: K_2CO_3 gave a poor conversion, while a clean double-coupling to **4** was observed with K_3PO_4. Fortunately, when Cs_2CO_3 in 1,4-dioxane was used, an excellent yield of the desired ynamide **3** was obtained. In all cases, we could not detect the formation of products resulting from monocoupling or from dehydrobromination of the starting material.

The coupling of (2,2-dibromovinyl)benzene with various nitrogen nucleophiles was next investigated using the optimized reaction conditions. Thus, a variety of ynamides were prepared and are shown in Table 1. Tosylamines, oxazolidinones, carbamates, and amides were all viable substrates and gave the corresponding ynamides in good to excellent yields. Interestingly, the replacement of 1,4-dioxane by DMF (for solubility purposes) had little effect on the outcome of the cross-coupling reaction. The conditions were mild enough so that an allyl group was well tolerated: no products resulting from an aza-Claisen rearrangement could be detected in the crude reaction mixture (Table 1, entry 2). In addition, the presence of bulky substituents on the nucleophile did not have a noticeable effect on the reaction (Table 1, entries 6 and 7). We found, however, that acyclic secondary amides were not suitable substrates, most likely because of their increased steric hindrance compared to their cyclic homologues and their lower acidity (Table 1, entry 14). The reaction is not

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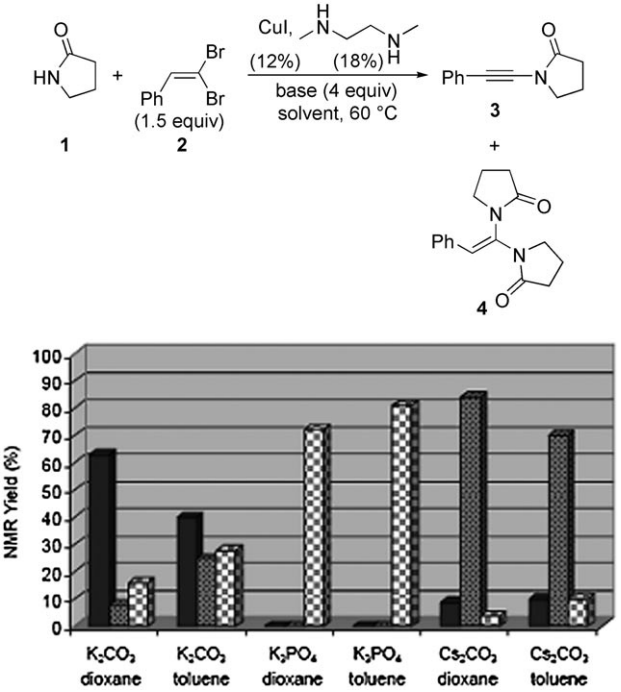


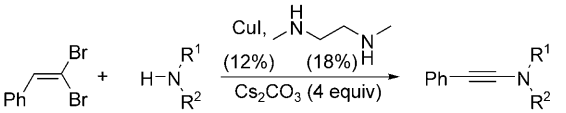
Figure 1. Optimization of the reaction conditions. Solid gray = compound **1**, dotted gray = compound **3**, squares = compound **4**.

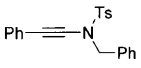
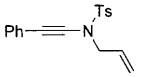
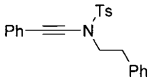
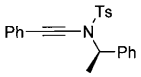
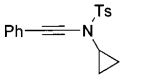
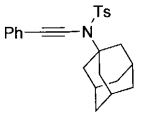
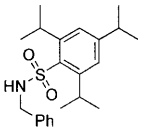
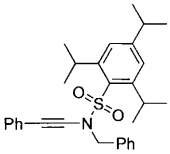
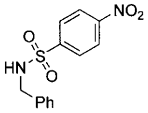
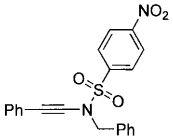
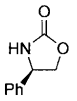
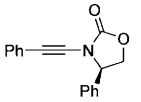
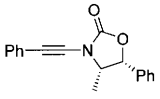
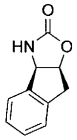
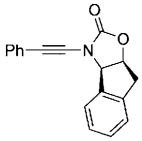
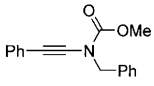
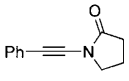
limited to the small scale (1.6 mmol) used for the coupling reactions described above as it could be conveniently performed on a 3 gram scale in 91% yield (Table 1, entry 1). In this case, a simple filtration of the reaction mixture, evaporation of the solvent, and removal of excess **2** by washing the crude solid residue with pentane afforded the corresponding ynamide in an analytically pure form.

The scope of the reaction was also investigated with respect to the aromatic 1,1-dibromo-1-alkene coupling partner (Table 2). The reaction was found to be compatible with a variety of aromatic groups, including heteroaromatic compounds (Table 2, entries 7–9). The presence of electron-withdrawing or donating groups had virtually no effect on the reaction (Table 2, entries 1–4 and 10–13). Notably, an aromatic chloride was tolerated on the dibromoalkene substrate and no competitive amination or reduction was observed (Table 2, entry 2). In general, tosylamines are more efficient coupling partners, as the preparation of ynamides from oxazolidinones and lactams was found to be more sluggish.

We next focused our attention on the reactivity of 2-alkyl- or 2-alkenyl-substituted 1,1-dibromo-1-alkenes (Table 3). As expected, the reaction was found to be more difficult and was best performed in DMF at 70 °C. Good yields of ynamide derivatives were obtained in most cases, even in the presence of bulky substitutents (Table 3, entries 10–13); in the cases of the less reactive pyrrolodin-2-one (Table 3, entries 9, 11, and 13) and acetaldehyde-derived dibromide (Table 3, entry 3) the ynamides were isolated in moderate yields. This protocol was however found to be general since a wide range of aliphatic and vinylic 1,1-dibromo-1-alkenes reacted successfully.

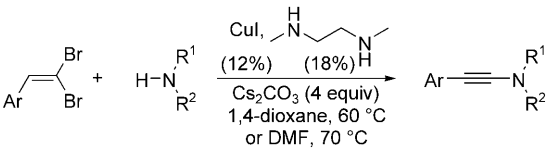
Table 1: Scope of the copper-mediated synthesis of ynamides from (2,2-dibromovinyl)benzene and various nitrogen nucleophiles.

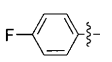
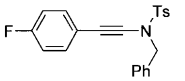
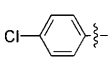
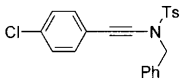
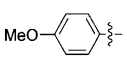
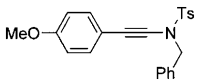
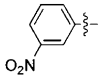
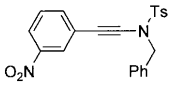
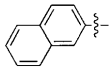
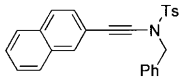
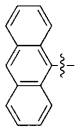
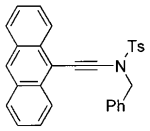
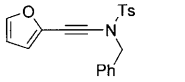
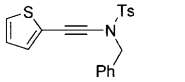
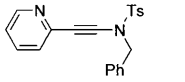
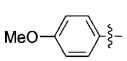
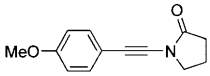
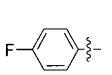
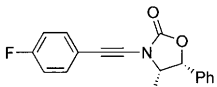
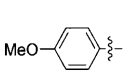
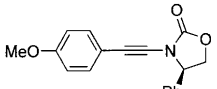
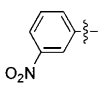
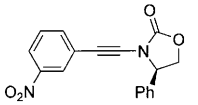


Entry	Nucleophile	Ynamide	Reaction conditions	Yield [%][a]
1			dioxane, 60 °C, 24 h	83, 91[b]
2			DMF, 60 °C, 48 h	81
3			dioxane, 60 °C, 24 h	93
4			dioxane, 60 °C, 24 h	83
5			dioxane, 60 °C, 48 h	79
6			dioxane, 60 °C, 24 h	77
7			DMF, 70 °C, 48 h	85
8			DMF, 70 °C, 48 h	82
9			dioxane, 60 °C, 24 h	82
10			DMF, 90 °C, 24 h	35
11			dioxane, 60 °C, 24 h	85
12			dioxane, 60 °C, 24 h	67
13			dioxane, 60 °C, 24 h	80
14		–	–	–

[a] Yield of product isolated after silica gel chromatography. [b] Yield of product for a reaction carried out on a 3 gram scale. Ts = 4-toluenesulfonyl, DMF = *N*,*N*-dimethylformamide.

Table 2: Scope of the copper-mediated synthesis of ynamides with aromatic 1,1-dibromo-1-alkenes.



Entry	Nucleophile	Aromatic or alkenyl	Ynamide	Yield [%][a]
1[b,d]				94
2[b,d]				77
3[b,d]				86
4[b,d]				94
5[c,e]				97
6[c,e]				86
7[b,e]				88
8[b,e]				66
9[b,e]				92
10[b,e]				66
11[b,e]				80
12[b,e]				55
13[b,d]				58

[a] Yield of product isolated after silica gel chromatography. [b] Reaction carried out in 1,4-dioxane at 60 °C. [c] Reaction carried out in DMF at 70 °C. [d] Reaction time was 24 hours. [e] Reaction time was 48 hours.

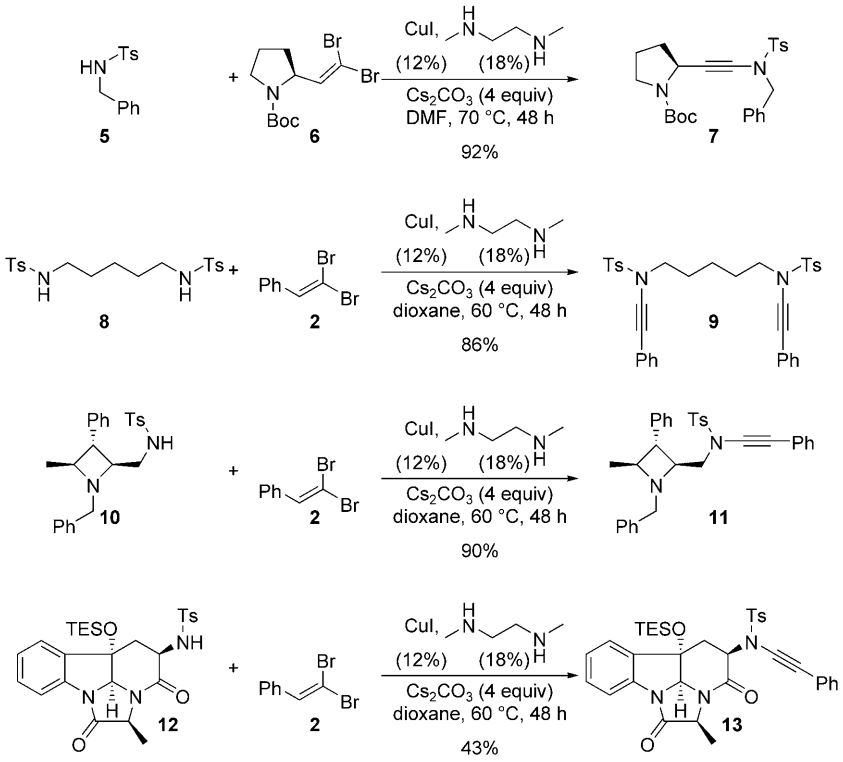
Table 3: Scope of the copper-mediated synthesis of ynamides with aliphatic and vinylic 1,1-dibromo-1-alkenes.

Entry	Nucleophile	Alkyl	Ynamide	Yield [%][a]
1[b]				84
2[b]				77
3		Me		25
4		Et		67
5		Et		65
6		C_5H_{11}		70
7[c]		C_8H_{17}		86
8[c]		C_8H_{17}		69
9		C_8H_{17}		43
10		*t*Bu		80
11		*t*Bu		34
12		Cy		70
13		Cy		43
14		TBDPSO		64

[a] Yield of product isolated after silica gel chromatography. [b] Reaction time was 24 hours. [c] Reaction carried out at 90 °C. Cy = cyclohexyl, TBDPS = *tert*-butyldiphenylsilyl.

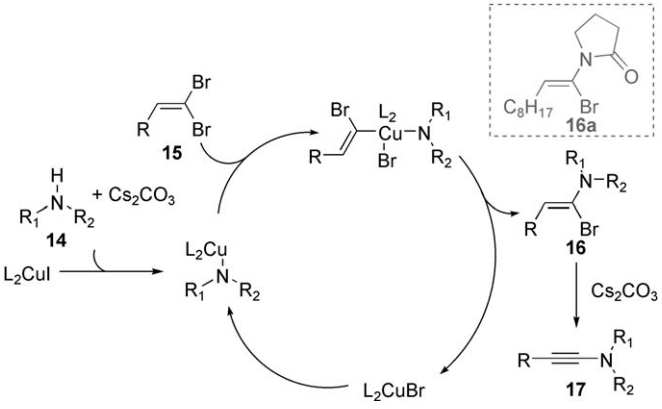
Finally, the formation of ynamides from complex substrates was evaluated to further test our procedure (Scheme 2). Proline-derived dibromide **6**[26] was smoothly converted into enantiopure ynamide **7**[26] in 92% yield. Notably, a double-coupling reaction performed on bis(tosylamine) **8** provided bis(ynamide) **9** in 86% yield, and tosyl azetidine **10**[27] was also found to be an excellent substrate. The transformation of **12**, which we recently used for the total synthesis of (−)-chaetominine,[19e] into **13** was less effective and resulted in an ynamide yield of 43%.

A possible simplified mechanism which accounts for the formation of ynamides **17** from 1,1-dibromo-1-alkenes **15** is



Scheme 2. Synthesis of ynamides from complex substrates. Boc = *tert*-butoxycarbonyl, TES = triethylsilyl.

shown in Scheme 3. This mechanism is based on the known higher reactivity of the *trans* C–Br bonds of dibromides **15** towards oxidative insertion[22] and would involve a regioselective coupling to yield **16**, whose subsequent dehydrobromination would then give the ynamide **17**. Fortunately, a (*Z*)-α-bromoenamide **16a** could be cleanly isolated in one case by lowering the reaction temperature[28] and was smoothly converted into the corresponding ynamide by reaction with Cs_2CO_3 in DMF at 70 °C. Another mechanism involving the formation of alkynyl bromides by dehydrobromination of the starting 1,1-dibromo-1-alkenes **15**[29] and its subsequent coupling to form ynamides **17** could also account for the



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

formation of the ynamides from 1,1-dibromo-1-alkenes. Since all attempts to evidence the formation of bromoalkynes from crude reaction mixtures failed and since their coupling typically requires either stronger bases or higher temperatures,[17] this hypothesis was discarded.

In conclusion, an efficient copper-mediated synthesis of ynamide derivatives has been described. This reaction has been shown to be general and provides a straightforward entry to ynamides that is complementary to previously reported synthetic routes. This method has the advantageous feature of starting from readily available 1,1-dibromo-1-alkenes, which are more attractive alkynylating agents than bromoalkynes or hypervalent iodonium salts. Further studies on the applications of this method and on the use of other nucleophiles will be reported in due course.

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