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Copper-mediated synthesis of *N*-vinyl ynamides from *N*-vinyl carbamates

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ABSTRACT

Ynamides are versatile 3-atoms building blocks for organic synthesis as they participate in a variety of ionic, radical and pericyclic processes. Converting ynamides into 5-atom building blocks, such as the yet unreported *N*-vinyl ynamides, would open new avenues in this fascinating chemistry. We describe herein our efforts towards such goal and demonstrate that the cross-coupling between *N*-vinyl carbamates and bromo-alkynes using copper(I) thiophene carboxylate, 1,10-phenanthroline and tBuOK in DMSO is a reactive system with an improved profile compared to the classical ynamides syntheses. The advantages and limitations of this copper-mediated reaction are discussed.

Ynamide π-systems can participate in a variety of pericyclic processes such as [4 + 2] and formal [4 + 2] cycloadditions, thus delivering structurally diverse nitrogen-containing heterocycles [1–6]. We have recently shown that ynamides could behave as competent electron-deficient dienophiles in intramolecular inverse electron demand Diels-Alder cycloadditions with pyrimidines, leading to complex 4-aminopyridines fused with a 5-membered ring after a spontaneous retro-[4 + 2] step (Scheme 1, A) [7–9].

Further investigations of this reaction, in particular of the connectivity within the cycloaddition precursor, demonstrated that 4-azaindolines such as **4** could be obtained in good yields when the nitrogen atom of the ynamide was placed *within* the tether between the azadiene and the dienophile (“internal” ynamides **3**, Scheme 1, B). The activation energy for this domino [4 + 2]/retro-[4 + 2] is not as high as for the “external” ynamides **1**, that required a temperature between 210 and 255 °C [7,8]. This promising result encouraged us to explore the scope of this transformation, as 4-azaindoles in general are relevant scaffolds for the chemical community and in particular for medicinal chemistry [10,11].

The main challenge in the synthesis of 4-azaindolines using this strategy was rapidly identified as the synthesis of the cycloaddition precursors themselves (such as **3**). Indeed, a preliminary screening of copper-mediated and copper-catalyzed reactions for the elaboration of the N-C7a σ-bond of ynamide **6** from β-ethylamino pyrimidines **5** led to dramatically poor yields (Scheme 1, C).

Indeed, established methods [2–6] were extensively screened using *gem*-dibromoalkenes, bromoalkynes or copper acetylides and *tert*-butyl (2-(4-(trifluoromethyl)pyrimidin-2-yl)ethyl)carbamate **5a** or *N*-((1-(4-(trifluoromethyl)pyrimidin-2-yl)cyclopropyl)-methyl)methanesulfonamide **5b**, leading to 10% yield of the desired ynamides **6a,b** in the best cases. Glaser type homocoupling was usually the major product of these cross-coupling reactions. This outcome could be logically attributed to the strongly coordinating effect of pyrimidines [12–14], which could lead to unproductive copper complexes (Scheme 1, C).

A second strategy for the synthesis of “internal” ynamides **6** would call for the construction of the C3-C3a σ-bond thanks to a transition metal-catalyzed cross-coupling reaction (Scheme 1, D). The reactive metallated intermediate would be obtained through a regio- and chemoselective hydrometallation reaction of *N*-vinyl ynamide **8**, itself prepared from the easily accessible (and commercially available in some cases) *N*-vinyl carbamate **7**. This strategy is reminiscent of previous research by Overman [15,16] who reported highly efficient hydroboration reaction/Suzuki cross-coupling of *N*-vinyl carbamates, although in the specific context of ynamide **8**, two π-systems would compete for the hydrometallation step.

Although *N*-vinyl ynamides **8** are not reported to the best of our knowledge, this class of ynamides combining two different π -systems whose electronics and sterics could be finely tuned, would represent a fascinating playground for a diversity of ionic or pericyclic reactions. We report herein the development of a copper-mediated synthesis of *N*-vinyl ynamides **6** that, although not of a

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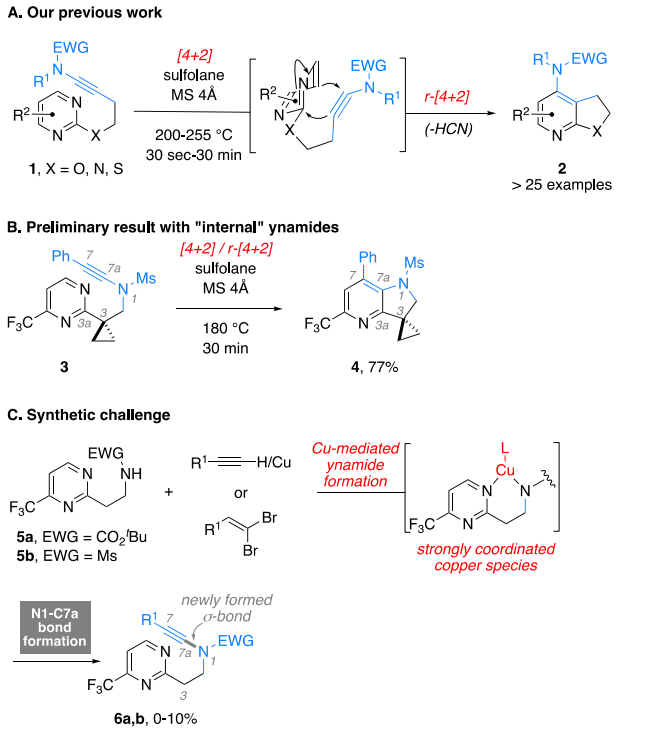
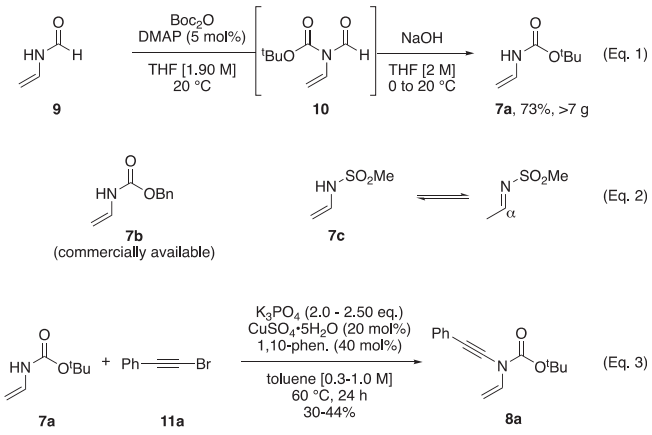


Scheme 1. Ynamides in inverse electron demand Diels-Alder cycloadditions (A, B), synthetic challenge associated with the cycloaddition precursors (C) and working hypothesis (D).

broad scope, allows the synthesis for the first time of these small and promising building blocks.

Synthesis of ynamides **6** relies first on an easy access to nitrogen nucleophiles **7** possessing an alkoxycarbonyl or a sulfonamide group as the electron-withdrawing substituent, as these motifs are the most classical protecting groups for ynamides nitrogen atoms. The synthesis of *N*-alkenyl carbamates has been achieved using copper(I)-catalyzed *N*-vinylation of carbamates [17,18] or transition-metal catalyzed isomerization of *N*-allylcarbamates [19,20]. When considering the simpler *N*-vinyl motif, two methods were reported relying on the Curtius rearrangement of acryloyl azide (followed by trapping with an alcohol) [21–24] or protection/deformylation of *N*-vinyl formamide **9** [25]. For practical reasons, we selected the latter method that delivered *N*-vinyl carbamate **7a** in good yield (Scheme 2, Eq. 1). Note that the corresponding benzyloxycarbamate **7b** is a commercially available compound (Scheme 2, Eq. 2) [26]. Also, it was observed that the synthesis of the corresponding *N*-vinyltosylamide **7c** proved impossible, which might be traced back to the high electrophilicity of the imine α-carbon, in equilibrium with the *N*-vinylsulfonamide [24,27].

Having in hand the desired nitrogen nucleophiles **7a,b**, we turned our attention to their reactivity in ynamide formation using known methods such as the ones reported by Evano, Stahl or Danheiser [2–6]. Unfortunately, no traces of the desired ynamides **8** could be detected; diyne formation arising from the copper-mediated Glaser homocoupling of the alkyne partner was observed as the only side product. The use of Hsung's conditions [2] on the

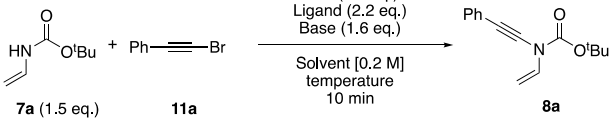


Scheme 2. Synthesis of *N*-vinyl carbamate **7a** (Eq. 1), availability of **7b** and unstability of **7c** (Eq. 2) and preliminary study of ynamide **8a** formation (Eq. 3).

other hand delivered **8a** in moderate yields (37 ± 7%) (Scheme 2, Eq. 3).

Unsatisfied by these moderate yields, we embarked on the screening of copper-mediated reaction conditions able to convert vinyl carbamates **7** to the corresponding *N*-vinyl ynamide **8** in good yields. Table 1 is a highlight of extensive research efforts that evaluated copper(I) salts, ligands, bases, solvents and temperatures, as well as the effect of syringe pump addition of the bromo-alkyne **11a** or *N*-vinyl carbamate **7**. Using copper thiophene carboxylate,

Table 1
Optimisation of the copper(I)-mediated C-N bond formation. [a]1.5 equiv. [b]3 equiv. [c]2.2 equiv. [d]Isolated yield.



Entry	CuX	Ligand	Base	Solvent	Temp. (°C)	NMR yield (%)
1	CuTC	1,10-phen.	tBuOK	THF	55	-
2	CuTC	1,10-phen.	tBuOK	NMP	55	-
3	CuTC	1,10-phen.	tBuOK	DMF	55	27
4	**CuTC**	**1,10-phen.**	**tBuOK**	**DMSO**	**55**	**75**
5	CuTC	-	tBuOK	DMSO	55	18
6	CuTC	*trans*-1,2-diaminocyclohexane	tBuOK	DMSO	55	-
7	CuTC	DMEDA	tBuOK	DMSO	55	-
8	CuTC	neocuproine	tBuOK	DMSO	55	-
9	CuTC	1,10-phen.	tBuOK	DMSO	40	74
10	CuTC	1,10-phen.	tBuONa	DMSO	55	68
11	CuI	1,10-phen.	tBuOK	DMSO	55	56
12	**CuTC[a]**	**1,10-phen.[b]**	**tBuOK[c]**	**DMSO**	**55**	**80 (71)[d]**