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Copper-Catalyzed Alkynylation of Amides with Potassium Alkynyltrifluoroborates: A Room-Temperature, Base-Free Synthesis of Ynamides

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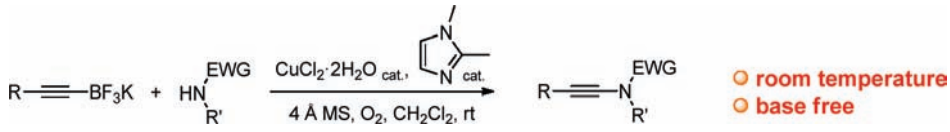
ABSTRACT



An efficient copper-mediated method for the coupling of potassium alkynyltrifluoroborates with nitrogen nucleophiles is reported. This reaction provides the first base-free and room-temperature synthesis of ynamides and allows for an easy preparation of these useful building blocks.

Heteroatom-substituted acetylenes probably represent the most versatile class of alkynes. An especially useful subgroup is the one containing a nitrogen atom directly attached to the triple bond: ynamides.[1] They display an exceptionally fine balance of stability and reactivity, offer unique and multiple opportunities for the inclusion of nitrogen-based functionalities into organic molecules, and are emerging as especially useful and versatile building blocks. The beginning of the 21st century has witnessed an ever increasing number of new reactions or synthetic sequences starting from ynamides[2] which have been used for the synthesis of various natural products[3] and for the rapid elaboration of complex scaffolds.

Over the past decades, the use of hypervalent alkynyliodonium salts as alkynylating agents[4] and the copper-catalyzed coupling of amides with alkynyl halides,[5] terminal alkynes,[6] 1,1-dihalo-1-alkenes,[7] or propiolic acids[8] have emerged as efficient strategies for the preparation of ynamides. While these procedures did clearly contribute to

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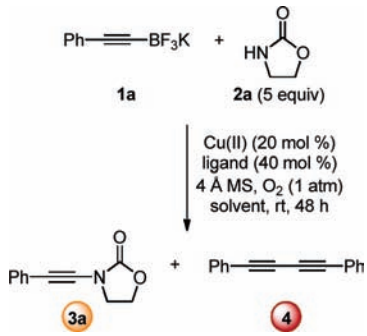
revitalizing the chemistry of nitrogen-substituted alkynes, general methods are still needed for ynamide formation, particularly since existing protocols often have limited substrate scope and typically require elevated temperatures, rigorous exclusion of air and/or water, and the use of a base.

Therefore, there is still a strong need for procedures that would allow for a room-temperature, base-free preparation of ynamides. Drawing from recent experiences in the field of copper-catalyzed cross-coupling reactions[9,10] and initially inspired by the work of the Batey group in the copper-catalyzed N-arylation[11] or vinylation[12] of amides, we thought that an efficient and attractive alternative for the preparation of ynamides would rely on the use of potassium alkynyl trifluoroborates as alkynyl transfer agents.[13] The tetracoordinate salts are readily prepared in a one-pot, two-step procedure from terminal alkynes. In addition to their high stability (to air, moisture, heating...), they have been shown to smoothly participate in various coupling reactions for the formation of C−C bonds.[14] However, there are still no reports on their use in cross-coupling involving heteroatoms, which could provide a straightforward entry to ynamides starting from N-nucleophiles. Herein we report that potassium alkynyltrifluoroborates can be used in copper-catalyzed cross-coupling with amides. These results represent the first catalytic synthesis of ynamides at room temperature and under base-free conditions.

Scheme 1. System Selected for the Optimization



We initiated our studies by examining the reaction of potassium phenylethynyltrifluoroborate **1a** and oxazolidinone **2a** as test substrates (Scheme 1). The influence of the solvent was first examined using 20 mol % of copper(II) acetate and 4 Å molecular sieves, without ligand, and under 1 atm of O_2 at rt (Figure 1). While the use of a highly polar solvent such as DMSO resulted in exclusive formation of the undesired homodimer **4**,[15] optimal results were observed when switching to dichloromethane where the low solubility of **1a** allows for a really low concentration of this reagent in the reaction mixture (ca. 5×10^{-3} mol/L) and notably reduces the amount of homodimer in favor of the desired ynamide **3a** which was still however formed in relatively low yield (10%).

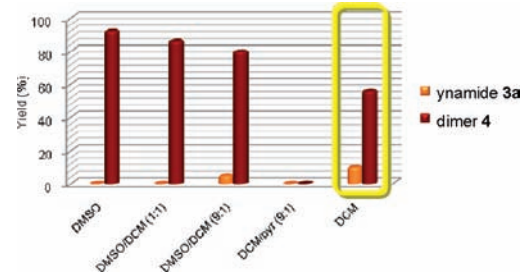


Figure 1. Solvent optimization. All reactions were carried out using 20 mol % of $Cu(OAc)_2 \cdot 2H_2O$, 4 Å MS, at 1 mol/L (based on **2a**), at rt, and under O_2 (1 atm) for 48 h.

Further screening of the catalytic reaction conditions involved examination of various ligands to promote the formation of the ynamide (Figure 2). While bidentate diamine $\mathbf{L_1}$, phenanthroline $\mathbf{L_2}$, or bipyridine $\mathbf{L_3}$ completely inhibited the reaction, its efficiency was greatly improved when using electron-rich monodentate ligands such as imidazoles[12] ($\mathbf{L_4}$−$\mathbf{L_6}$) or benzimidazoles ($\mathbf{L_7}$−$\mathbf{L_9}$), the most efficient one being 1,2-dimethylimidazole (DMI, $\mathbf{L_6}$) which allowed for the isolation of ynamide **3a** in 51% yield together with 38% of diyne **4**.

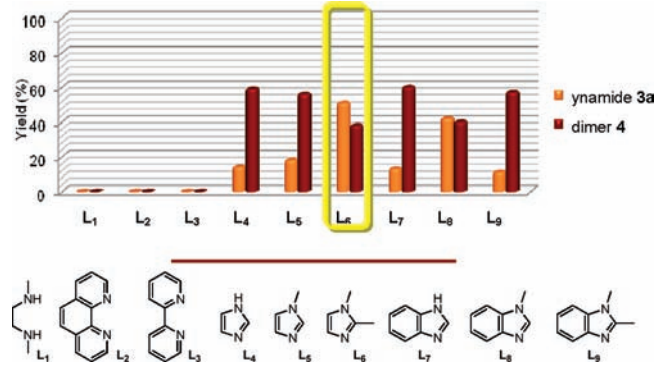


Figure 2. Ligand optimization. All reactions were carried out using 20 mol % of $Cu(OAc)_2 \cdot 2H_2O$, 40 mol % of ligand, 4 Å MS, in DCM at 1 mol/L (based on **2a**), at rt, and under O_2 (1 atm) for 48 h.

The outcome of the reaction was finally examined using various copper(II) salts (Figure 3), which turned out to be a

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crucial parameter. While $Cu(CO_3)$ and $Cu(acac)_2$ were found to be totally inefficient, the homodimer was still formed predominantly with $Cu(OTf)_2$, and no differences were observed with $Cu(OAc)_2{\cdot}2H_2O$, $Cu(SO_4){\cdot}5H_2O$, or $Cu(NO_3)_2{\cdot}3H_2O$. It was not until $CuCl_2{\cdot}2H_2O$ was used that the ynamide **3a** could be isolated in 71% yield with almost complete suppression of homocoupling. Using this salt, catalyst loading could be slightly decreased to 15 mol %: the use of lower amounts did not allow for full conversion.

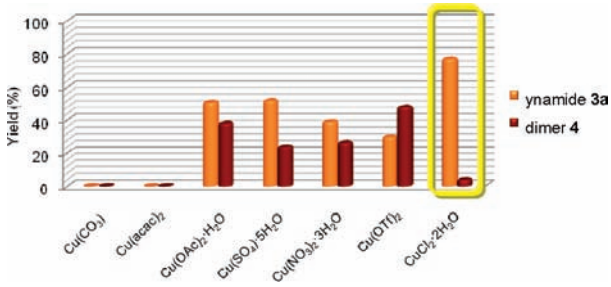

Figure 3. Optimization of the copper source. 20 mol % of Cu(II), 40 mol % of 1,2-dimethylimidazole, 4 Å MS, in DCM at 1 mol/L (based on **2a**), at rt, and under O_2 (1 atm) for 48 h.

Interestingly, other complexes such as $PdCl_2(CH_3CN)_2$ or $FeCl_3$ did not catalyze the reaction: even if the counteranion for copper clearly plays a crucial role in the reaction, other metals do not work as well and copper is clearly really needed.

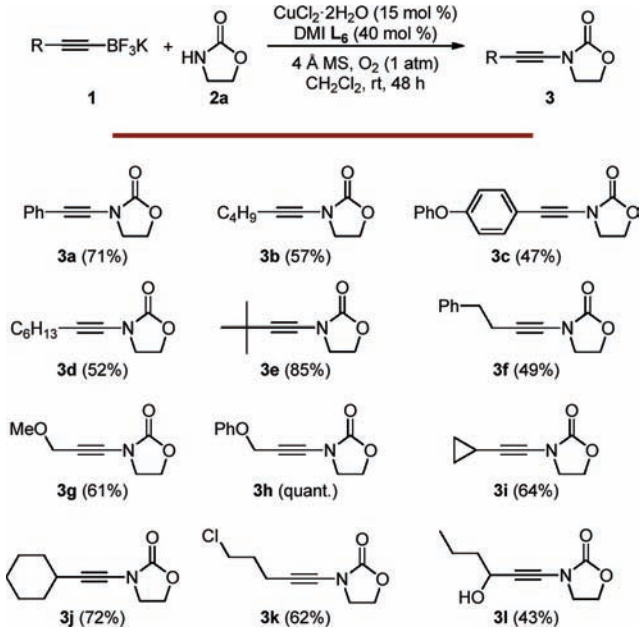

Figure 4. Copper-catalyzed alkynylation of oxazolidinone with potassium alkynyltrifluoroborates.

The coupling of oxazolidinone **2a** with various potassium alkynyltrifluoroborates **1** was next investigated using our optimized conditions. Thus, a variety of ynamides were prepared in moderate-to-good yields and are shown in Figure 4. The reaction is compatible with a variety of aromatic- and alkyl-substituted alkynyltrifluoroborates, even in the presence of a bulky substituent. Notably, propargyl alcohol derivatives (**3g** and **3h**), aliphatic chlorides (**3k**), and even free alcohols (**3l**) are tolerated.

The reaction scope was also investigated with respect to the N-nucleophile using two representative trifluoroborates **1a** and **1b** (Figure 5). Oxazolidinones, imidazolidinones, and tosylamines, including *N*-tosylaniline, were shown to react smoothly and gave the corresponding ynamides **5**−**10** and **12**−**14** in good yields. For reasons that are still unclear, pyrrolidinone did not perform as well as other nucleophiles, and the corresponding ynamides **11a** and **11b** were obtained in lower yields. The reaction was however found to be rather general and allowed for the synthesis of a wide range of ynamides possessing representative substitution patterns, including TMS-substituted ynamides (**15**).

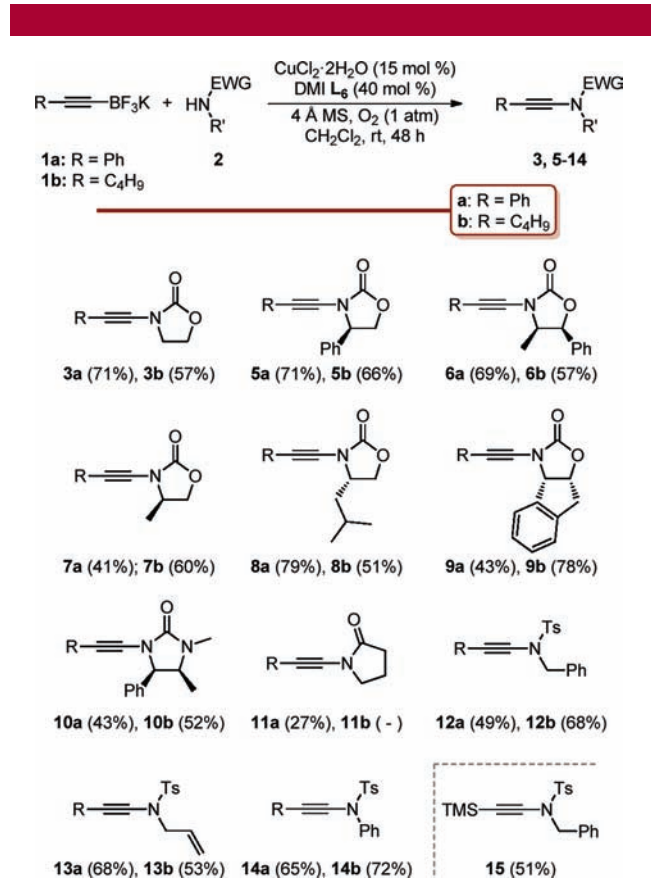

Figure 5. Copper-catalyzed alkynylation of N-nucleophiles with potassium phenylethynyl and hex-2-ynyl trifluoroborates.

Finally, the reaction is not limited to the small scale used for the coupling described above and could conveniently be performed on a gram scale for compounds **3a** and **12b** in comparable yields.

In conclusion, we have developed an efficient copper-mediated method for the coupling of potassium alkynyltri-

fluoroborates with nitrogen nucleophiles. This reaction provides the first base-free and room-temperature synthesis of ynamides and allows for an easy preparation of these useful building blocks. Further studies on the use of other nucleophiles will be reported in due course.

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Supporting Information Available: Experimental procedures, characterization, and copies of ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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