Communication

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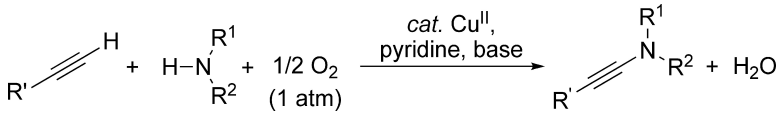

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Copper-Catalyzed Aerobic Oxidative Amidation of Terminal Alkynes: Efficient Synthesis of Ynamides

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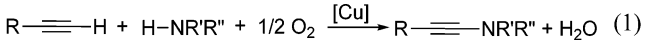
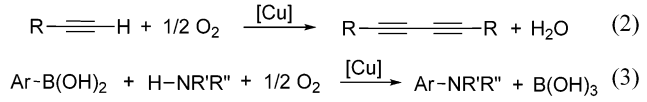
Metal-catalyzed cross-coupling reactions are among the most powerful methods available for the formation of carbon−carbon and carbon−heteroatom bonds.[1,2] Oxidative-coupling reactions, particularly methods that enable direct functionalization of C−H bonds, have been the focus of significant recent interest.[3] Unfortunately, such methods often require stoichiometric oxidants that reduce their appeal relative to classical cross-coupling reactions. Our interest in aerobic oxidation reactions[4] prompted us to consider Cu-catalyzed oxidative coupling reactions that could employ molecular oxygen as the stoichiometric oxidant, and we describe here a new Cu-catalyzed method for the synthesis of ynamides via direct amidation of the C−H bond of terminal alkynes (eq 1). The reactions exhibit quite a broad scope with respect to the alkyne and nitrogen nucleophile, and O_2 may be used as the stoichiometric oxidant. The utility of ynamides as synthons in organic chemistry has expanded significantly in recent years,[5,6] and ynamide preparation via oxidative coupling represents an efficient alternative to known two-step methods, such as involving alkyne halogenation followed by C−N cross-coupling (Scheme 1).[7,8]



(1)

Two important precedents provided a basis for our investigation of the alkyne amidation reactions: (1) the Glaser−Hay oxidative dimerization of alkynes (eq 2)[9] and (2) the oxidative coupling of arylboronic acids and nitrogen nucleophiles, first reported by Chan and Lam (eq 3).[10,11] These results suggested that, under appropriate



(2)

(3)

conditions, aerobic oxidative cross-coupling of alkynes and nitrogen nucleophiles might be possible. Hints of such reactivity are evident in the literature,[12,13] but several recent examples of metal-catalyzed oxidative amination of alkynes yield carboxamides rather than ynamides.[14] The present results represent the first catalytic synthesis of ynamides directly from alkynes.

We initiated our studies by examining the reaction of phenylacetylene (**1a**) with 2-oxazolidinone (**2a**) in the presence of stoichiometric copper salts under 1 atm of O_2. In our initial screening of Cu sources, Brønsted bases and solvents, optimal results were observed with 2 equiv of $CuCl_2$ and Cs_2CO_3 in dimethylsulfoxide (DMSO) (Table 1, entries 1−4).[15a] When the substrates were combined in a 1:1 ratio, we observed the formation of **3a** together with the homocoupled dimer **4** and alkynyl chloride **5** (entry 1).[16] The yield of **3a** was enhanced, and side products were reduced by increasing the quantity of nitrogen nucleophile to 5 equiv (entries 2−4) and by adding the alkyne to the reaction mixture over a period of 4 h (entry 4). When the copper loading was reduced to 20 mol %, good yields of **3a** were obtained by replacing Cs_2CO_3 with $NaHCO_3$ as the base (entries 5 and 6). Further screening of the catalytic reaction conditions revealed that

Scheme 1. Copper-Catalyzed Pathways for Ynamide Synthesis

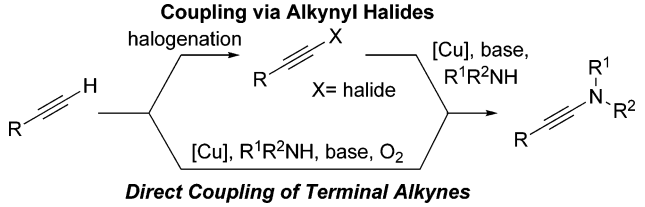
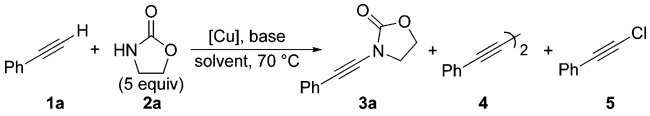


Table 1. Selected Screening Results for Copper-Mediated Oxidative Coupling of Phenylacetylene and 2-Oxazolidinone

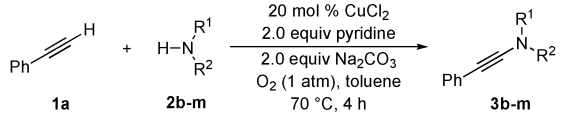


entry	reaction conditions (equiv of reagents)[a]	solvent	% yield[b] **3a (4/5)**
1	$CuCl_2$ (2), Cs_2CO_3 (2), 1 equiv **2a**[c]	DMSO	26 (42/17)
2	$CuCl_2$ (2), Cs_2CO_3 (2)[c]	DMSO	53 (24/4)
3	$CuCl_2$ (2), Cs_2CO_3 (2)[d]	DMSO	70 (28/−)
4	**$CuCl_2$ (2), Cs_2CO_3 (2)**	**DMSO**	**89 (4/−)**
5	$CuCl_2$ (0.2), Cs_2CO_3 (2)	DMSO	trace (19/−)
6	$CuCl_2$ (0.2), $NaHCO_3$ (2)	DMSO	90 (4/−)
7	$CuCl_2$ (0.2), $NaHCO_3$ (2)	toluene	46 (2/−)
8	$CuCl_2$ (0.2), $NaHCO_3$ (2), pyridine (0.4)	toluene	60 (2/−)
9	$CuCl_2$ (0.2), $NaHCO_3$ (2), pyridine (0.8)	toluene	64 (2/−)
10	$CuCl_2$ (0.2), $NaHCO_3$ (2), pyridine (2)	toluene	85 (2/−)
11	$CuCl_2$ (0.2), $NaHCO_3$ (2), phen[e] (0.2)	toluene	43 (26/−)
12	$CuCl_2$ (0.2), $NaHCO_3$ (2), bpy[e] (0.2)	toluene	68 (17/−)
13	$CuCl_2$ (0.2), $NaHCO_3$ (2), DMED[e] (0.2)	toluene	65 (7/−)
14	$CuCl_2$ (0.2), $NaHCO_3$ (2), 2-ACH[e] (0.2)	toluene	48 (3/−)
15	$CuCl_2$ (0.2), $NaHCO_3$ (2), DMAP[e] (2)	toluene	53 (2/−)
16	$CuCl_2$ (0.2), $NaHCO_3$ (2), CF_3py[e] (2)	toluene	65 (3/−)
17	**$CuCl_2$ (0.2), Na_2CO_3 (2), pyridine (2)**	**toluene**	**89 (2/−)**
18	$CuCl_2$ (0.2), Na_2CO_3 (2), pyridine (2), 1 equiv **2a**	toluene	69 (16/4)
19	$CuBr_2$ (0.2), Na_2CO_3 (2), pyridine (2)	toluene	81 (2/−)
20	$Cu(OAc)_2$ (0.2), Na_2CO_3 (2), pyridine (2)	toluene	88 (3/−)
21	$Cu(TFA)_2$[e] (0.2), Na_2CO_3 (2), pyridine (2)	toluene	73 (3/−)

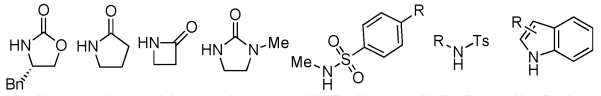
[a] Standard conditions: 0.1 mmol **1a**, 0.5 mmol **2a**, 1 atm O_2, 1 mL of solvent, 70 °C. 4 h; phenylacetylene added dropwise to the reaction mixture over 4 h. [b] **3a**: isolated yields; **4** and **5**: GC yields. [c] Alkyne added in a single aliquot. [d] Alkyne added to the solution over 1 h. [e] Abbreviations: phen = phenanthroline; bpy = 2,2′-bipyridine; DMED = *N*,*N*′-dimethylethylenediamine; 2-ACH = 2-Ac-cyclohexanone; DMAP = 4-*N*,*N*-dimethylaminopyridine; CF_3py = 4-trifluoromethylpyridine; TFA = trifluoroacetate.

toluene was also a suitable solvent if nitrogen donor ligands were included in the reaction mixture (entries 7−21). Optimal conditions featured 20 mol % $CuCl_2$ and 2 equiv of Na_2CO_3 and pyridine (entry 17). A useful yield of **3a** (69%) was also obtained under catalytic conditions with a **1a**:**2a** ratio of 1:1. As expected, a higher yield of diyne byproduct **4** is formed under these conditions (16%); however, this result is significant for the synthesis of ynamides with nitrogen nucleophiles that are not commercially available.[17] Chelating ligands that have been used in other Cu-catalyzed C−N

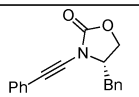
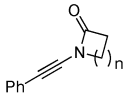
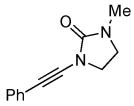
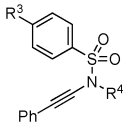
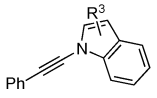
Table 2. Cu-Catalyzed Oxidative Coupling of Phenylacetylene with Nitrogen Nucleophiles[a]



Nitrogen Nucleophiles:



2b **2c** **2d** **2e** **2f**: R= Me **2g**: R= NO_2 **2h**: R= OMe **2i**: R= Bn **2j**: R= *n*-Bu **2k**: R= 3-Ac **2l**: R= 3-CO_2Me **2m**: R= 2-CO_2Et

entry	R^1R^2NH	Ynamide		% yield[b]
1	**2b**		**3b**	82
2	**2c**		**3c** (n= 2)	trace
3	**2d**		**3d** (n= 1)	89
4	**2e**		**3e**	79
5	**2f**		**3f** (R^3, R^4 = Me)	93
6	**2g**		**3g** (R^3 = NO_2, R^4 = Me)	86
7	**2h**		**3h** (R^3 = OMe, R^4 = Me)	92
8	**2i**		**3i** (R^3 = Me, R^4 = Bn)	68
9	**2j**		**3j** (R^3 = Me, R^4 = *n*-Bu)	79
10	**2k**		**3k** (R^3 = 3-Ac)	78
11	**2l**		**3l** (R^3 = 3-CO_2Me)	89
12	**2m**		**3m** (R^3 = 2-CO_2Et)	56

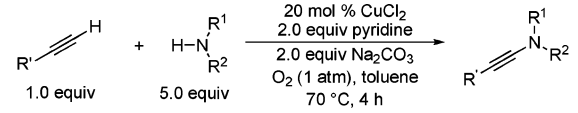
[a] Reaction conditions: 0.1 mmol **1a**, 0.5 mmol R^1R^2NH, 0.2 mmol Na_2CO_3, 0.02 mmol $CuCl_2$, 0.2 mmol pyridine, toluene (1.0 mL), 1 atm O_2, 70 °C, **1a** added to the reaction over a 4-h period. [b] Isolated yields.

coupling reactions (entries 11−14)[2d−f] and pyridine derivatives (entries 15 and 16) led to inferior results. Among the Cu sources tested, both $CuCl_2$ and $Cu(OAc)_2$ were effective and performed better than $CuBr_2$ and $Cu(O_2CCF_3)_2$.

The oxidative coupling of phenylacetylene with various nitrogen nucleophiles was examined with 2 equiv of $CuCl_2$ in DMSO and 20 mol % $CuCl_2$ in toluene. The results under catalytic conditions were consistently better than those obtained under stoichiometric conditions[15b] and led to moderate-to-excellent isolated yields of the alkynamide products (Table 2). Cyclic carbamate, amide, and urea nucleophiles gave the desired ynamides in high yield (entries 1, 3, and 4). For reasons that are not yet clear, pyrrolidinone is an ineffective nucleophile under these conditions (entry 2); however, a 55% yield of the desired product could be obtained with stoichiometric $CuCl_2$ in DMSO.[15b] Acyclic nucleophiles, including *N,O*-dimethylcarbamate, acetanilide, and *N,N′*-dimethylurea, showed almost no reactivity under either set of conditions. 4-Substituted-*N*-alkyl benzenesulfonamides afforded ynamides in moderate-to-high yields (entries 5−9), and indoles with substituents at the 2- or 3-position were also viable substrates (entries 10−12).

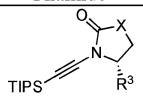
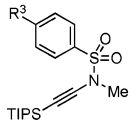
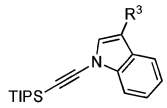
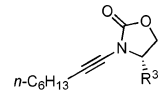
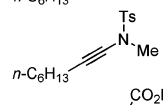
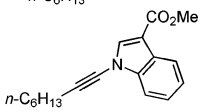
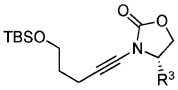
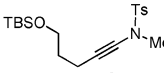
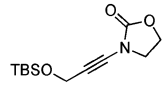
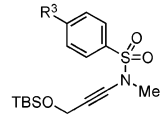
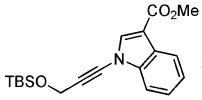
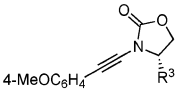
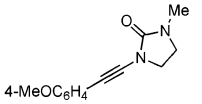
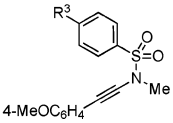
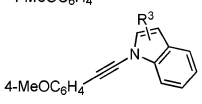
The reaction scope was also investigated with respect to the alkyne coupling partner (Table 3). Once again, the use of catalytic conditions in toluene typically led to higher yields than the stoichiometric conditions in DMSO.[15b] The reaction is compatible with a variety of different terminal alkynes, including alkyl-, aryl-, and silyl-substituted alkynes. TBS-protected hydroxyalkyl analogues, including propargyl alcohol derivatives, are effective. In general, electron-rich alkynes are more effective coupling partners. For example, triisopropylsilylacetylene reacts successfully with

Table 3. Cu-Catalyzed Oxidative Amidation of Alkynes[a]



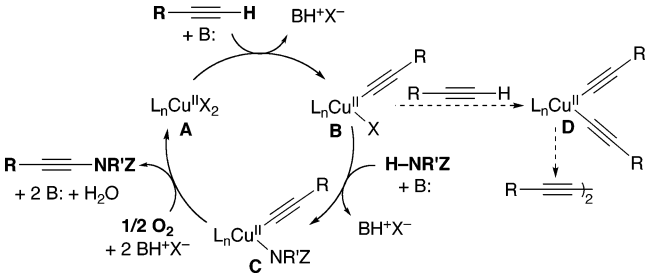
Alkynes: R' = TIPS [TIPS = (i-Pr)$_3$Si] (**1b**), n-C_6H_{13} (**1c**), $TBSO(CH_2)_3$ (TBS = t-BuMe$_2$Si) (**1d**), $TBSOCH_2$ (**1e**), 4-$MeOC_6H_4$ (**1f**)

Nitrogen Nucleophiles: **2a - 2m** (see Table 2)

entry	Alkyne	R^1R^2NH	Ynamide		% Yield[b]
1	**1b**	**2a**		**6** (X= O, R^3= H)	83
2		**2b**		**7** (X= O, R^3= Bn)	78
3		**2c**		**8** (X= CH_2, R^3= H)	95
4		**2e**		**9** (X= NMe, R^3= H)	70
5		**2f**		**10** (R^3= Me)	87
6		**2g**		**11** (R^3=NO_2)	85
7		**2h**		**12** (R^3= OMe)	87
8		**2k**		**13** (R^3= Ac)	62[c]
9		**2l**		**14** (R^3=CO_2Me)	90[c]
10	**1c**	**2a**		**15** (R^3= H)	72
11		**2b**		**16** (R^3= Bn)	80
12		**2f**		**17**	87
13		**2l**		**18**	63
14	**1d**	**2a**		**19** (R^3= H)	75[c]
15		**2b**		**20** (R^3= Bn)	66
16		**2f**		**21**	77
17	**1e**	**2a**		**22**	78
18		**2f**		**23** (R^3= Me)	83
19		**2g**		**24** (R^3= NO_2)	82
20		**2l**		**25**	81
21	**1f**	**2a**		**26** (R^3= H)	81
22		**2b**		**27** (R^3= Bn)	84
23		**2e**		**28**	80
24		**2f**		**29** (R^3= Me)	97
25		**2g**		**30** (R^3=NO_2)	86
26		**2h**		**31** (R^3= OMe)	94
27		**2k**		**32** (R^3= 3-Ac)	78
28		**2l**		**33** (R^3= 3-CO_2Me)	90
29		**2m**		**34** (R^3= 2-CO_2Et)	51

[a] Reaction conditions: 0.1 mmol alkyne, 0.5 mmol R^1R^2NH, 0.2 mmol Na_2CO_3, 0.02 mmol $CuCl_2$, 0.2 mmol pyridine, toluene (1.0 mL), 1 atm O_2, 70 °C, The alkyne was added to the reaction over a 4 h period. [b] Isolated yields. [c] Obtained with the stoichiometric $CuCl_2$/DMSO system; see SI for details.

Scheme 2. Mechanistic Proposal for Copper-Catalyzed Oxidative Coupling of Terminal Alkynes and Nitrogen Nucleophiles



pyrrolidinone (entry 3), an ineffective nucleophile in the reaction with phenylacetylene (see above); the corresponding ynamide was obtained in high yield (95%). Electron-deficient alkynes, such as ethylpropiolate and 4-nitrophenylacetylene, were less effective, resulting in ynamide yields of ≤10% and 35%, respectively, with oxazolidinone as the nucleophile.

The reactions are not limited to the small scale described above (i.e., 0.1 mmol). Ynamides **3a**, **3f**, and **10** were successfully prepared on 1 mmol scale in yields comparable to or higher than those on small scale (91%, 98%, and 85%, respectively), and ynamide **3f** was prepared on 10 mmol scale (85% yield).[15a]

The mechanism of this reaction remains to be elucidated. The formation of alkynyl chlorides as side products in the reaction raises the possibility that C−N bond formation could arise from Cu-mediated cross-coupling of an alkynyl chloride and a nitrogen nucleophile. Attempts to use alkynyl chlorides directly as substrates, however, resulted in negligible yields of ynamide. Therefore, we postulate a catalytic mechanism that features sequential activation of the alkyne and nitrogen nucleophile, followed by C−N reductive elimination and aerobic reoxidation of the catalyst (Scheme 2). This mechanism rationalizes the beneficial effect of using excess equivalents of the nitrogen nucleophile: formation of the mixed Cu^{II}(alkynyl)(amidate) species **C** is expected to compete directly with activation of a second equivalent of alkyne to form bis-alkynyl-Cu^{II} species **D**. The latter intermediate will produce the undesired diyne byproduct. Factors that contribute to the success (or failure) of different nitrogen nucleophiles are presently poorly understood, although the substrate pK_a presumably plays an important role. Nucleophiles effective in the reactions above exhibit a pK_a in the range of 15−23 (DMSO); however, not all substrates with a pK_a in this range, including pyridone (17.0) and acetanilide (21.5), are effective. Systematic investigation of these issues will be the focus of future studies.

In conclusion, we have developed a copper-catalyzed method for aerobic oxidative coupling of terminal alkynes with a variety of nitrogen nucleophiles. The reactions provide efficient access to ynamides and provide a benchmark for the development of new aerobic oxidative coupling reactions.

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Supporting Information Available: Experimental details, additional screening data, and characterization data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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