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Copper-Mediated N-Alkynylation of Carbamates, Ureas, and Sulfonamides. A General Method for the Synthesis of Ynamides

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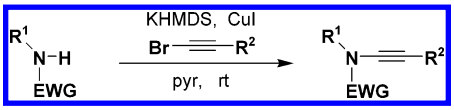
ABSTRACT



A general amination strategy for the N-alkynylation of carbamates, sulfonamides, and chiral oxazolidinones and imidazolidinones is described. A variety of substituted ynamides are available by deprotonation of amides with KHMDS followed by reaction with CuI and an alkynyl bromide.

We report herein a convenient and general method for the synthesis of ynamides via the copper-promoted coupling of amides with alkynyl bromides. Interest in the application of ynamides in organic synthesis has increased enormously in recent years.[1] Considerably more robust than simple ynamines, ynamides are more easily stored and handled and tolerate a variety of conditions destructive to typical ynamines. Ynamides have thus emerged as versatile building blocks in a wide range of useful synthetic transformations including Pauson−Khand reactions,[2] ring-closing metatheses,[3] cycloadditions (and other ring-forming processes),[4] and a variety of hydrometalation and hydrohalogenation reactions.[5,6]

In connection with our studies on [4 + 2] cycloadditions of conjugated enynes[7] and heteroenynes,[8] we required an efficient method for the preparation of a wide range of ynamides, preferably via the direct alkynylation of carbamates, sulfonamides, and other simple amide derivatives. Initially we focused our attention on the reaction of metalated amides with alkynyl(phenyl)iodonium salts (eq 1).[9] Stang[10] and Feldman[11] have shown that this process provides an excellent route to "push−pull"-type ynamides (**4**, Z = COR,

(1) For reviews of the chemistry of ynamines and ynamides, see: (a) Mulder, J. A.; Kurtz, K. C. M.; Hsung, R. P. *Synlett* **2003**, 1379. (b) Zificsak, C. A.; Mulder, J. A.; Hsung, R. P.; Rameshkumar, C.; Wei, L.-L. *Tetrahedron* **2001**, *57*, 7575. (c) Himbert, G. In *Methoden der Organischen Chemie (Houben-Weyl)*; Kropf, H., Schaumann, E., Eds.; Georg Thieme Verlag: Stuttgart, 1993; Vol. E15, Part 3, pp 3267−3443. (d) Collard-Motte, J.; Janousek, Z. *Top. Curr. Chem.* **1986**, *130*, 89.

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(6) Also see: (a) Tanaka, R.; Hirano, S.; Urabe, H.; Sato, F. *Org. Lett.* **2003**, *5*, 67. (b) Mulder, J. A.; Hsung, R. P.; Frederick, M. O.; Tracey, M. R.; Zificsak, C. A. *Org. Lett.* **2002**, *4*, 1383. (c) Frederick, M. O.; Hsung, R. P.; Lambeth, R. H.; Mulder, J. A.; Tracey, M. R. *Org. Lett.* **2003**, *5*, 2663.

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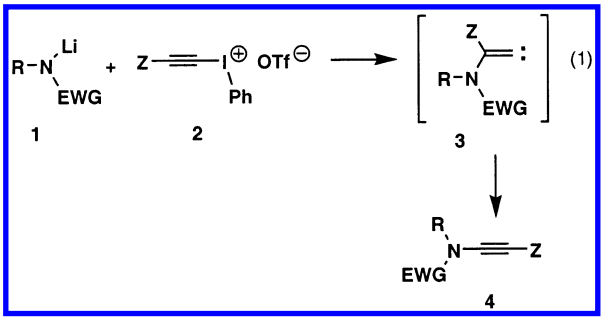
CO_2R, SO_2Ar, etc.), and more recently Witulski and Rainier have extended this chemistry to the preparation of ynamides where Z = hydrogen, TMS, and phenyl.[2a−d,4b] Unfortunately, this approach is not applicable to the synthesis of ynamides in which Z is a simple alkyl group. The addition of soft nucleophiles to alkynyl(phenyl)iodonium salts is believed to proceed via the rearrangement of alkylidenecarbene intermediates of type **3**, and the requisite 1,2-shift only is a facile process when Z is a hydrogen atom or trialkylsilyl or aryl group.[12] In addition, whereas sulfonamide derivatives (e.g., **1**, EWG = Ts) participate smoothly in the desired transformation, reactions of lactams,[1a] oxazolidinones,[1a] and acyclic carbamates[13] proceed at best in low yield.

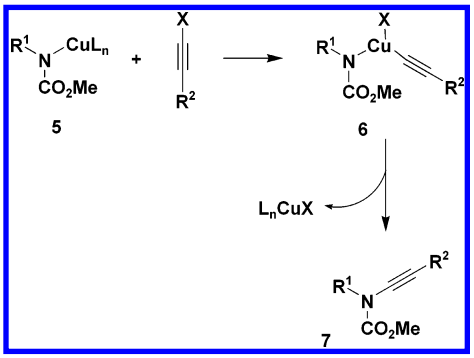


The aforementioned limitations of alkynyl(phenyl)iodonium methodology prompted us to consider alternative and potentially more general approaches to the synthesis of the ynamides required for our studies. Recent developments in the laboratories of Buchwald and Hartwig have revolutionized methodology for carbon−nitrogen bond formation.[14] Encouraged, in particular, by Buchwald's recent success in achieving copper-catalyzed amidation of aryl halides,[15,16] we turned our attention to the coupling of amide derivatives with readily available alkynyl *halides*.[17]

Initial results were disappointing. Application of Buchwald's catalyst system[15] to the coupling of acyclic carbamates with 1-bromo-2-phenylacetylene gave only trace amounts of the desired ynamide, with the predominant product being the 1,3-diyne generated from "homocoupling" of the alkynyl halide. During the course of our work, an important communication by Hsung and co-workers appeared reporting the successful application of Buchwald's catalyst system[15] to the N-alkynylation of oxazolidinones and lactams.[18,19] Unfortunately, Hsung found these conditions to be less effective when applied to other amide derivatives, including *acyclic* carbamates and sulfonamides. Thus, under the Buchwald protocol ureas and sulfonamides undergo alkynylation in less than 10% yield. Somewhat better results are obtained in the case of carbamates; by terminating reactions at 30−50% conversion, Hsung and co-workers were able to isolate the desired ynamides, albeit in only 24−42% yield.

Our first success in effecting the desired alkynylation was achieved when we turned our attention to protocols in which complete conversion of the amide substrate to its copper derivative (e.g., **5**) was carried out *prior* to addition of the alkynyl halide. Under these conditions, copper-promoted dimerization of the alkynyl halide is greatly diminished and the desired ynamides emerge as the major product of the reaction. As outlined in Scheme 1, oxidative addition of **5** to the alkynyl halide presumably generates a copper(III) intermediate **6**, which then furnishes the desired ynamide by reductive elimination. Preforming the copper amide intermediate **5** maximizes the rate of its reaction with the alkynyl halide, allowing amidation to more effectively compete with the reaction of the alkynyl halide with copper salts in pathways leading to "homodimer" byproducts.

Scheme 1



A systematic investigation of reaction variables using carbamate **8a** as the test substrate led to the protocol outlined in Scheme 2. Under these conditions, 1-bromo-2-phenylacetylene undergoes amidation in 48% yield. Note that this bromo alkyne is especially prone to homocoupling, and in

(11) Feldman, K. S.; Bruendl, M. M.; Schildknegt, K.; Bohnstedt, A. C. *J. Org. Chem.* **1996**, *61*, 5440.

(12) In the case where Z is an acyl or sulfonyl group, it is not clear if a 1,2-shift is involved or whether the mechanism proceeds via an addition−elimination pathway.

(13) Our attempts to alkynylate acyclic carbamates (**1**, R = alkyl, EWG = CO_2Me) with **2** (Z = $SiMe_3$) produced the desired ynamides **4** in 15−20% yield.

(14) For recent reviews, see: (a) Muci, A. R.; Buchwald, S. L. *Top. Curr. Chem.* **2002**, *219*, 131. (b) Hartwig, J. F. *Angew. Chem., Int. Ed.* **1998**, *37*, 2046.

(15) Klapars, A.; Huang, X.; Buchwald, S. L. *J. Am. Chem. Soc.* **2002**, *124*, 7421. The Buchwald procedure for amidation of aryl bromides involves reaction with 0.01−0.1 equiv of CuI, 2 equiv of K_3PO_4, and 0.1 equiv of a diamine ligand in toluene or dioxane at 110 °C for 15−24 h.

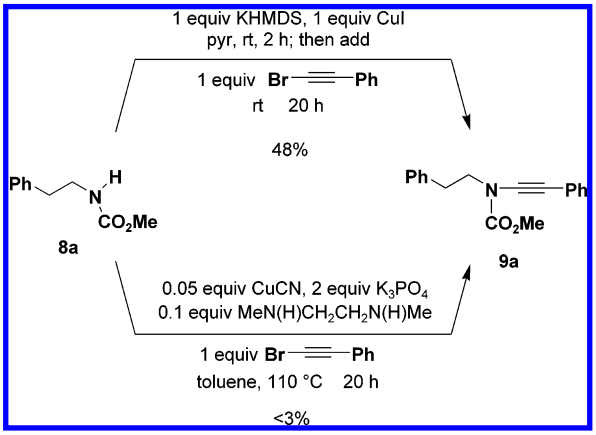
(16) Also encouraging were recent reports on the preparation of enamides and enamines via amidation and amination of vinyl halides and triflates. See: (a) Ogawa, T.; Kiji, T.; Hayami, K.; Suzuki, H. *Chem. Lett.* **1991**, 1443. (b) Shen, R.; Porco, J. A. *Org. Lett.* **2000**, *2*, 1333. (c) Arterburn, J. B.; Pannala, M.; Gonzalez, A. M. *Tetrahedron Lett.* **2001**, *42*, 1475. (d) Barluenga, J.; Fernández, M. A.; Aznar, F.; Valdés, C. *J. Chem. Soc., Chem. Commun.* **2002**, 2362. (e) Kozawa, Y.; Mori, M. *Tetrahedron Lett.* **2002**, *43*, 111. (f) Lebedev, A. Y.; Izmer, V. V.; Kazyul'kin, D. N.; Beletskaya, I. P.; Voskoboynikov, A. Z. *Org. Lett.* **2002**, *4*, 623. (g) Willis, M. C.; Brace, G. N. *Tetrahedron Lett.* **2002**, *43*, 9085.

(17) For reviews of the chemistry of halo acetylenes, see: (a) Hopf, H.; Witulski, B. In *Modern Acetylene Chemistry*; Stang, P. J., Diederich, F., Eds.; VCH: Weinheim, 1995; pp 33−66. (b) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: New York, 1988.

(18) Frederick, M. O.; Mulder, J. A.; Tracey, M. R.; Hsung, R. P.; Huang, J.; Kurtz, K. C. M.; Shen, L.; Douglas, C. J. *J. Am. Chem. Soc.* **2003**, *125*, 2368.

(19) For two early reports of the observation of copper-promoted formation of ynamines and ynamides from reactions of amine derivatives with *terminal* alkynes, see: (a) Peterson, L. I. *Tetrahedron Lett.* **1968**, *9*, 5357. (b) Balsamo, A.; Macchia, B.; Macchia, F.; Rossello, A.; Domiano, P. *Tetrahedron Lett.* **1985**, *26*, 4141.

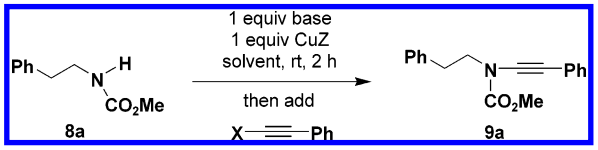
Scheme 2



our hands the application of Buchwald's catalyst system (as reported by Hsung[18]) afforded <3% of the desired ynamide **9a**. Also notable is the observation that under our conditions the reaction proceeds smoothly *at room temperature*, in contrast to the elevated temperatures (110−150 °C) required in the Buchwald and Hsung amidations.

As summarized in Table 1, acetylenic iodides also participate in the alkynylation, whereas chloro alkynes are significantly less reactive and undergo amidation only upon heating and then in poor yield (entries 1−3). As expected, somewhat improved yields are observed when 2 equiv of alkynyl halides are employed to compensate for losses due to homocoupling (compare entries 2 and 9).[20] Interestingly,

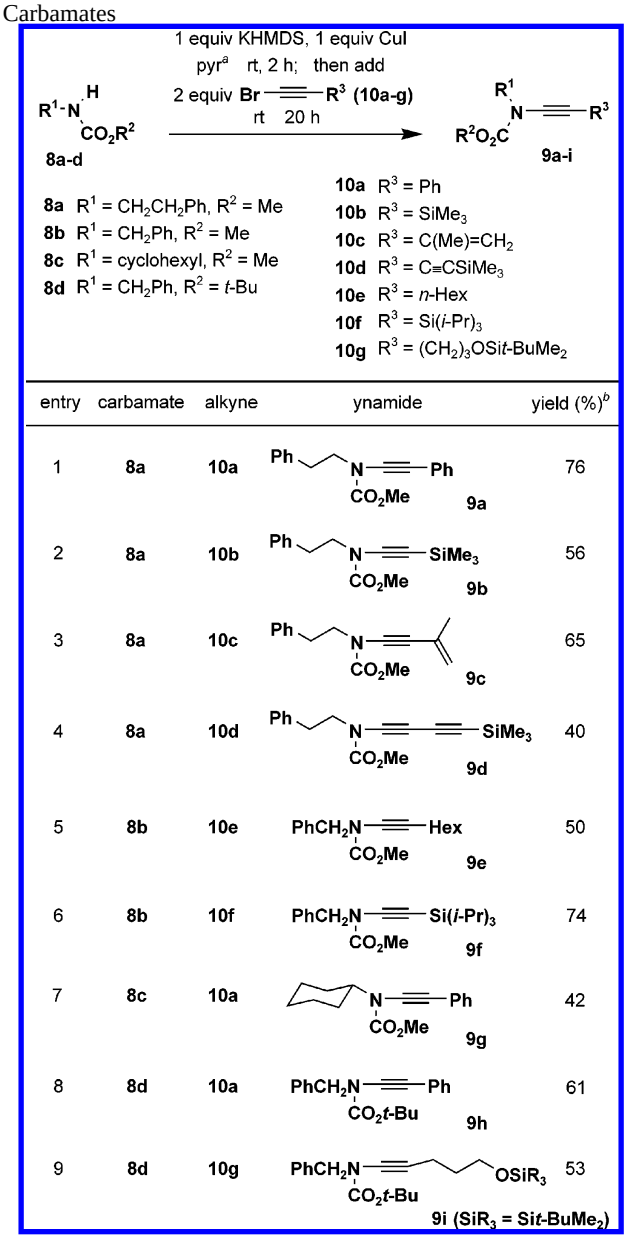
Table 1. Optimization of Alkynylation Conditions[a]



entry	base	CuZ	solvent	alkyne equiv, X	yield (%)[b]
1	KHMDS	CuI	pyr	1.0, I	44
2	KHMDS	CuI	pyr	1.0, Br	48
3	KHMDS	CuI	pyr[c]	1.0, Cl	23
4	KHMDS	CuI	DMF	1.0, Br	26
5	*n*-BuLi	CuI	pyr	1.0, Br	0
6	*n*-BuLi	CuI	DMSO	1.0, Br	20
7	*n*-BuLi	CuTC[d]	DMSO	1.0, Br	24
8	KHMDS	CuI	pyr	0.6, Br	40[e]
9	**KHMDS**	**CuI**	**pyr**	**2.0, Br**	**67[f]**
10	KHMDS	CuCN	pyr	2.0, Br	41
11	KHMDS	CuI	tol, diamine[g]	2.0, Br	40
12	KHMDS	CuI	pyr	5.0, Br	28[h]

[a] All reactions were carried out at rt for 20 h unless otherwise indicated. Concentration of **8a** (0.200 g scale) was 0.15 M. Alkynes were added as benzene solutions. [b] Isolated yields of products purified by column chromatography. [c] Reaction at 75 °C. [d] Copper(I) thiophene-2-carboxylate. [e] Yield based on 1-bromo-2-phenylethyne. [f] Yield improved to 76% when scale increased to 2.0 g of **8a**. [g] 4.0 equiv of diamine ligand MeN(H)CH_2-CH_2N(H)Me. [h] Reaction for 90 h.

Table 2. Synthesis of Ynamides by Alkynylation of Carbamates



entry	carbamate	alkyne	ynamide	yield (%)[b]
1	**8a**	**10a**	Ph, N, Ph, CO_2Me **9a**	76
2	**8a**	**10b**	Ph, N, $SiMe_3$, CO_2Me **9b**	56
3	**8a**	**10c**	Ph, N, CO_2Me **9c**	65
4	**8a**	**10d**	Ph, N, $SiMe_3$, CO_2Me **9d**	40
5	**8b**	**10e**	$PhCH_2N$, Hex, CO_2Me **9e**	50
6	**8b**	**10f**	$PhCH_2N$, $Si(i\text{-}Pr)_3$, CO_2Me **9f**	74
7	**8c**	**10a**	N, Ph, CO_2Me **9g**	42
8	**8d**	**10a**	$PhCH_2N$, Ph, $CO_2t\text{-}Bu$ **9h**	61
9	**8d**	**10g**	$PhCH_2N$, $OSiR_3$, $CO_2t\text{-}Bu$ **9i** (SiR_3 = Sit-BuMe$_2$)	53

[a] KHMDS was added as a solution in THF and the alkynyl bromide was added as a solution in benzene. [b] Isolated yields of products purified by column chromatography.

pyridine proved to be the most effective solvent for the alkynylation reaction, clearly superior to the toluene−diamine ligand system (entry 11) employed by Buchwald[15] and Hsung[18] in their amidation studies. Under our optimal conditions (entry 9), the desired ynamide is obtained in 67% yield, with the yield increasing to 76% when the reaction is carried out on a multigram scale.[21]

Table 2 details the scope of the N-alkynylation reaction as applied to acyclic carbamates. A broad range of substituted

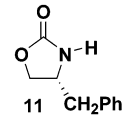
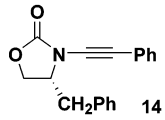
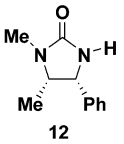
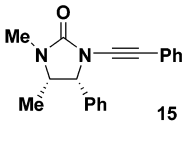
(20) Interestingly, Hsung found that the yields of ynamides *decrease* when more than 1 equiv of alkynyl halide is employed under the Buchwald amidation conditions (which are catalytic in copper salt); see Supporting Information in ref 18.

and functionalized alkynyl bromides participate in the reaction, including systems especially prone to homocoupling such as the bromo derivatives of conjugated enynes and diynes. Note also that these conditions provide access to ynamides **9e** and **9f** in yields considerably better than that reported by Hsung[18] using the Buchwald catalyst system.

As summarized in Table 3, we have also found that our alkynylation protocol can be applied with good results to several other classes of amide derivatives. Notably, both imidazolidinones and sulfonamides undergo N-alkynylation in good yield. Both classes of amides are exceedingly poor substrates in alkynylations with the Buchwald catalyst system,[18] and alkynyl sulfonamides such as **17** bearing alkyl substituents on the acetylene cannot be prepared via alkynyl(phenyl)iodonium methodology (vide supra).

In summary, we have developed a general procedure for the copper-promoted N-alkynylation of a variety of amide derivatives that is complementary to the catalytic process recently introduced by Hsung and co-workers. Hsung's protocol offers the advantage of requiring only a catalytic amount of copper salt but requires reaction at elevated temperatures (110−150 °C) and is not applicable to the efficient synthesis of ynamides from certain important classes of amides such as sulfonamides and acyclic carbamates. Our alkynylation reaction proceeds at room temperature and can be applied to a broad range of substrates but does require a full equivalent of (relatively inexpensive) copper iodide. Both methods have the advantageous feature of employing alkynyl bromides, which are easily prepared by bromination of terminal acetylenes, and thus represent more attractive alkynylating agents than alkynyl(phenyl)iodonium salts.

Table 3. N-Alkynylation of Sulfonamides and Cyclic Carbamates and Ureas[a]

entry	amide	alkyne	ynamide	yield (%)[b]
1	 **11**	**10a**	 **14**	74
2	 **12**	**10a**	 **15**	60
3	$PhCH_2NHTs$ **13**	**10a**	$PhCH_2N(Ts)$—≡—Ph **16**	78
4	$PhCH_2NHTs$ **13**	**10e**	$PhCH_2N(Ts)$—≡—Hex **17**	42

[a] Amide was treated with 1 equiv each of KHMDS and CuI in pyridine−THF (rt, 2 h); 2 equiv of bromo alkyne in benzene was then added, and the reaction mixture was stirred at rt for 20 h. [b] Isolated yields of products purified by column chromatography.

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Supporting Information Available: Experimental procedures and characterization data for all alkynylation reactions and ynamide products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(21) **Typical Experimental Procedure.** A 250-mL, two-necked, round-bottomed flask equipped with a rubber septum and addition funnel fitted with a rubber septum and argon inlet needle was charged with carbamate **8a** (1.951 g, 10.89 mmol) and 44 mL of pyridine. The solution was cooled at 0 °C while 12.0 mL of KHMDS solution (0.91 M in THF, 11 mmol) was added via syringe over 4 min. The reaction mixture was stirred at 0 °C for 10 min, and then a solution of CuI (2.073 g, 10.89 mmol) in 22 mL of pyridine was added via cannula in one portion (10-mL pyridine rinse). The ice bath was removed, and the resulting solution was stirred at room temperature for 2 h. A solution of bromo alkyne **10a** (36 mL, 0.60 M in benzene, 22 mmol) was then added via the addition funnel over 1 h, and the resulting mixture was stirred at room temperature for 20 h. The reaction mixture was diluted with 300 mL of Et_2O and washed with three 100-mL portions of a 2:1 mixture of saturated NaCl solution and concentrated NH_4OH. The combined aqueous layers were extracted with three 75-mL portions of Et_2O, and the combined organic layers were washed with 300 mL of saturated NaCl solution, dried over $MgSO_4$, filtered, and concentrated to provide 4.397 g of a dark red oil. Column chromatography on 120 g of silica gel (gradient elution with 0−3% EtOAc−hexanes) furnished 2.309 g (76%) of ynamide **9a** as a yellow oil.