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Copper-Catalyzed Coupling of Imines, Acid Chlorides, and Alkynes: A Multicomponent Route to Propargylamides

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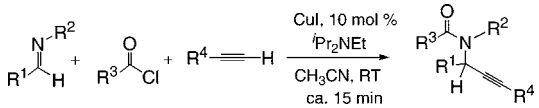
ABSTRACT



The use of imines in a metal-catalyzed coupling with alkynes and acid chlorides is described. This process proceeds rapidly with CuI as the catalyst and provides an efficient and general three-component coupling method to prepare propargylamides. The coupling can also be diversified to allow the formation of *N*-carbamate-protected propargylamines with the use of chloroformates.

Multicomponent coupling reactions have become of growing relevance in the development of efficient new syntheses.[1,2] When coupled with the reactivity of metal catalysts, this approach can be particularly effective in the conversion of simple building blocks directly into important functional subunits.[3] One useful family of products toward which this approach has yet to be applied are propargylamides. These compounds represent the core of a range of biologically relevant molecules (e.g., oxotremorine,[4] dynemicin precursors,[5] and various herbicides and fungicides[6]) and are useful substrates in the synthesis of heterocycles[7] and biomimetic polymers.[8]

Traditional routes to prepare propargylamides include the Ritter reaction of olefins with nitriles,[9] or the addition of nucleophilic acetylides to imines,[10] followed by acylation. The stringent conditions, lack of functional group compatibility, and limited reagent diversity do provide limitations to these processes. Recently, a range of efficient and mild metal-catalyzed reactions based upon the nucleophilic addition of in situ generated metal acetylides to imines or *N*,*N*-dialkyliminium salts have been reported for the synthesis of

(1) For reviews, see: (a) Armstrong, R. W.; Combs, A. P.; Tempest, P. A.; Brown, S. D.; Keating, T. A. *Acc. Chem. Res.* **1996**, *29*, 123−131. (b) Ugi, I.; Domling, A.; Werner, B. *J. Heterocycl. Chem.* **2000**, *37*, 647−658. (c) Weber, L.; Illgen, K.; Almstetter, M. *Synlett* **1999**, *3*, 366−374.

(2) Classical examples of MCRs: (a) Ugi, I.; Steinbrueckner, C. *Chem. Ber.* **1961**, *94*, 2802−2814. (b) Strecker, A. *Ann. Chem.* **1850**, *75*, 27−45. (c) Mannich, C.; Kösche, W. *Arch. Pharm. (Weinheim, Ger.)* **1912**, *250*, 647−667. (d) Hantzsch, A. *Ber. Dtsch. Chem. Ges.* **1890**, *23*, 1474−1476.

(3) Representative examples: (a) Beller, M.; Eckert, M. *Angew. Chem., Int. Ed.* **2000**, *39*, 1010−1027. (b) Montgomery, J. *Acc. Chem. Res.* **2000**, *33*, 467−473. (c) Dhawan, R., Dghaym, R. D., Arndtsen, B. A. *J. Am. Chem. Soc.* **2003**, *125*, 1474−1475. (d) Kamijo, S.; Jin, T.; Huo, Z.; Yamamoto, Y. *J. Am. Chem. Soc.* **2003**, *125*, 7786−7787. (e) Tessier, P. E.; Penwell, A. J.; Souza, F. E. S.; Fallis, A. G. *Org. Lett.* **2003**, *5*, 2989−2992. (f) Trost, B. M.; Pinkerton, A. B. *J. Am. Chem. Soc.* **2000**, *122*, 8081−8082. (g) Cao, C.; Shi, Y.; Odom, A. L. *J. Am. Chem. Soc.* **2003**, *125*, 2880−2881. (h) Rao, I. N.; Prabhakaran, E. N.; Das, S. K.; Iqbal, J. *J. Org. Chem.* **2003**, *68*, 4079−4082.

(4) Dahlborn, R. In *Cholinergic Mechanisms: Phylogenetic Aspects, Central and Peripheral Synapses, and Clinical Significance*; Pepeu, G., Ladinsky, H., Eds.; Plenum Press: New York, 1981; pp 621−638.

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(6) Swithenbank, C.; McNulty, P. J.; Viste K. L. *J. Agr. Food Chem.* **1971**, *19*, 417−421.

(7) (a) Nilsson, B. M.; Hacksell, U. *J. Heterocycl. Chem.* **1989**, *26*, 269−275 and references therein. (b) Arcadi, A.; Cacchi, S.; Cascia, L.; Fabrizi, G.; Marinelli, F. *Org. Lett.* **2001**, *3*, 2501−2504. (c) Harvey, D. F.; Sigano, D. M. *J. Org. Chem.* **1996**, *61*, 2268−2272.

(8) (a) Tabei, J.; Nomura, R.; Masuda, T. *Macromolecules* **2002**, *35*, 5405−5409. (b) Gao, G.; Sanda, F.; Masuda, T. *Macromolecules* **2003**, *36*, 3932−3937.

(9) Ritter, J. J.; Minieri, P. P. *J. Am. Chem. Soc.* **1948**, *70*, 4045−4048.

(10) (a) Volkmann, R. A. In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Pergamon Press: Oxford, 1991; Vol. 1, pp 360−373. (b) Bloch, R. *Chem. Rev.* **1998**, *98*, 1407−1438.

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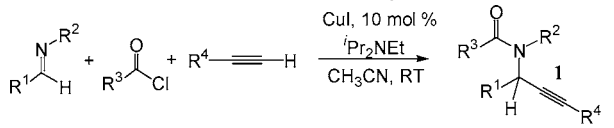
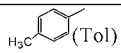
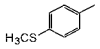
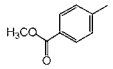
the related propargylamines.[10−16] Examples of these reactions include the metal-catalyzed coupling of alkynes with imines,[11] the copper-mediated addition of alkynes to enamines,[12] and more recently, the metal-catalyzed multicomponent condensation of aldehydes and amines with zinc acetylides[13] or alkynes.[14] In addition, Li has recently reported the synthesis of propargylcarbamates via a related alkyne addition to presynthesized α-sulfonylcarbamates with stoichiometric amounts of copper salts.[17] To our knowledge, however, a metal-catalyzed reaction to directly prepare propargylamides, and in a fashion amenable to structural diversification, has not been reported.

We have recently demonstrated that imines can be activated toward oxidative addition to Pd(0) and a Stille-type coupling with organotin reagents by the addition of acid chlorides,[18,19] providing a useful method to use multiply bonded electrophiles in cross-coupling reactions. In light of the mechanistic similarity of Stille couplings (transmetalation from organotin reagents) to Sonogashira couplings (transmetalation from an in situ formed copper acetylide),[20,21] we considered the possibility that a similar reaction could provide a route to couple alkynes to imines. We describe below the results of these efforts, which have led to the development of a method to assemble propargylamides directly from three readily available building blocks: imines, acid chlorides, and alkynes. This modular approach can be generalized to the preparation of N-protected propargylamines, as well as the direct alkyne addition to N-heterocyclic compounds.

Our initial efforts toward this coupling examined the simultaneous reaction of benzoyl chloride, phenylacetylene, and *N*-benzyltolylaldimine in the presence of $Pd_2(dba)_3$·$CHCl_3$ (5 mol %), CuI (10 mol %), and the base $^iPr_2NEt$. Monitoring the reaction by ^1H NMR reveals the rapid consumption of the reactants at ambient temperature. More importantly, examination of the reaction mixture reveals the clean formation of propargylamide **1** (Table 1, entry 1). This coupling is essentially quantitative, with **1** representing the only observable reaction product (>95% NMR yield).[22]

Table 1. Copper-Catalyzed Three-Component Coupling of Imines, Acid Chlorides, and Terminal Alkynes[a]



#	R^1	R^2	R^3	R^4	%[b]
1[c]		Bn	Ph	Ph	(95)
2	Tol	Bn	"	Ph	(98) 82
3		Et	"	Ph	87
4[d]		Bn	"	TMS	77
5[d]		Bn	"	TMS	86
6		Bn	"	Ph	92
7	Tol	$CH_2CO_2CH_3$	"	Ph	87
8[e]	Tol	Bn	CH_3	Ph	76
9		Et		Ph	81
10	Tol	Bn		Ph	84
11		Bn		Ph	93
12	Tol	Ph	Ph	Ph	99
13	"	Et	"	CH_2Cl	84
14[f]	"	Bn	"	CH_2OTMS	90
15	"	"	"	CH_2OAc	89
16	"	"	"	n-C_4H_9	93
17[d]	"	"	"	TMS	99

[a] 0.48 mmol of imine, 0.63 mmol of acid chloride, 0.48 mmol of alkyne, 0.72 mmol of $^iPr_2NEt$, and 0.048 mmol of CuI in CH_3CN (7 mL), 15−60 min. [b] (NMR yield) isolated yield. [c] 5 mol % Pd_2dba_3·$CHCl_3$ present. [d] 2 h. [e] Base added last to minimize ketene formation. [f] Isolated as hydroxypropargylamide.

In an effort to further simplify this methodology, the importance of both catalysts (Pd(0) and Cu(I)) was examined. Performing a similar transformation with Pd(0) catalyst but without CuI leads to no reaction, consistent with the need for CuX to activate the alkyne toward coupling (vide infra). However, copper complexes themselves are known to mediate certain cross-coupling reactions in a fashion similar to palladium[20a,23] as well as the direct alkyne addition to iminium salts.[10−17] Indeed, this three-component coupling proceeds quite efficiently with 10 mol % CuI as the sole catalyst (entry 2, Table 1). The rates of the coupling are

(11) (a) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2002**, *124*, 5638−5639. (b) Fischer, C.; Carreira, E. M. *Org. Lett.* **2001**, *3*, 4319−4321. (c) Li, C.-J.; Wei, C. *Chem. Commun.* **2002**, 268−269.

(12) (a) Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2002**, *41*, 2535−2538. (b) Brannock, K. C.; Burpitt, R. D.; Thweatt, J. G. *J. Org. Chem.* **1963**, *28*, 1462−1464.

(13) (a) Akullian, L. C.; Snapper, M. L.; Hoveyda, A. H. *Angew. Chem., Int. Ed.* **2003**, *42*, 4244−4247. (b) Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2003**, *5*, 3273−3275.

(14) (a) Wei, C.; Li, C.-J. *J. Am. Chem. Soc.* **2003**, *125*, 9584−9585. (b) Gommermann, N.; Koradin, C.; Polborn, K.; Knochel, P. *Angew. Chem., Int. Ed.* **2003**, *42*, 5763−5766. (c) Youngman, M. A.; Dax, S. L. *Tetrahedron Lett.* **1997**, *38*, 6347−6348.

(15) For other examples, see: (a) Frantz, D. E.; Fässler, R.; Carreira, E. M. *J. Am. Chem. Soc.* **1999**, *121*, 11245−11246. (b) Ukaji, Y.; Kenmoku, Y.; Inomata, K. *Tetrahedron: Asymmetry* **1996**, *7*, 53−56.

(16) For related multicomponent syntheses of α-substituted amines, see: Porter, J. R.; Traverse, J. F.; Hoveyda, A. H.; Snapper, M. L. *J. Am. Chem. Soc.* **2001**, *123*, 10409−10410, and references therein.

(17) Zhang, J.; Wei, C.; Li, C.-J. *Tetrahedron Lett.* **2002**, *43*, 5731−5733.

(18) Davis, J. L.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2004**, *43*, 590−594.

(19) Unlike imines, *N*-acyl iminium salts are prone to oxidative addition to form metal-chelated amides: (a) Severin, K.; Bergs, R.; Beck, W. *Angew. Chem., Int. Ed.* **1998**, *37*, 1634−1654. (b) Dghaym, R. D.; Dhawan, R.; Arndtsen, B. A. *Angew. Chem., Int. Ed.* **2001**, *40*, 3228−3230.

(20) (a) Sonogashira, K. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E., Ed.; John Wiley and Sons: New York, 2002; Vol. 1, pp 493−529. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467−4470.

(21) Diederich, F.; Stang, P. *Metal Catalyzed Cross-Coupling Reactions*; Wiley-VCH: New York, 1998.

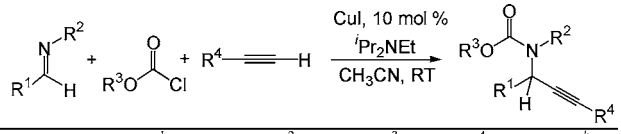
(22) Ketone products from a direct coupling of acid chloride with the in situ generated copper acetylides are not observed (vide infra).

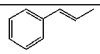
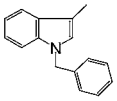
(23) For examples, see: (a) Okuro, K.; Furuune, M.; Enna, M.; Miura, M.; Nomura, M. *J. Org. Chem.* **1993**, *58*, 4716−4721. (b) Piers, E.; Wong, T. *J. Org. Chem.* **1993**, *58*, 3609−3610. (c) Allred, G. D.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748−2749. (d) Falck, J. R.; Bhatt, R. K.; Ye, J. *J. Am. Chem. Soc.* **1995**, *117*, 5973−5982.

similarly rapid (<15 min) both with and without palladium present, suggesting that in both instances the copper salt is the active catalyst. Other copper sources have also been found to be competent catalysts ($CuPF_6$, CuCN, CuCl), and the presence of bidentate phosphine (dppe) or nitrogen (2,2′-bipyridyl) ligands does not significantly inhibit the reaction. In addition to nitrogen bases ($^iPr_2NEt$ or NEt_3), inorganic bases such as K_3PO_4 can also be employed, though the latter does lead to a more sluggish reaction (18 h).

A useful feature of this three-component coupling is the nature of the building blocks employed, each of which can be easily varied (Tables 1 and 2). In addition to electron-rich and electron-poor C-aryl-substituted imines (Table 1, entries 1−4), imines derived from heteroaryl aldehydes (entry 5), α,β-unsaturated imines (Table 1, entry 11), and even the less electrophilic C-alkyl imines (Table 1, entry 6) all react to form propargylamides in high yields. The reaction is tolerant of various functional groups, including thioether, ester, furanyl, halide, and indoyl units (entries 3−5 and 9, Table 1; entry 3, Table 2). Similar alkyl and aryl diversity can be incorporated onto the imine nitrogen (Table, 1, entries 12−14) and acid chloride (entries 8−11), as can imines derived from α-amino acids (entry 7). However, the use of enolizable imines does not lead to an appreciable quantity of product, due to their rapid conversion to enamides under the basic reactions conditions.[24] The alkyne unit is also readily generalized, with electron-rich (entries 16, 17), electron-poor (entry 4, Table 2), and functionalized (Table 1, entries 13−15) alkynes all forming propargylamides in good yields. In general, this level of diversity is high compared to the metal-catalyzed alkynylation of imines themselves,[11] and even standard Sonogashira couplings (which are typically sluggish with electron poor alkynes),[20a] and can be attributed to the ability of acid chlorides to activate imines toward a facile coupling (vide infra). Overall, considering the mild reaction conditions (ambient temperature), the building blocks employed (alkynes, imines, acid chlorides), and the commercial availability of the catalyst (CuI), this multicomponent methodology represents a straightforward route to construct propargylamides.

Table 2. Copper-Catalyzed Synthesis of N-Carbamate Protected Propargylamines[a]



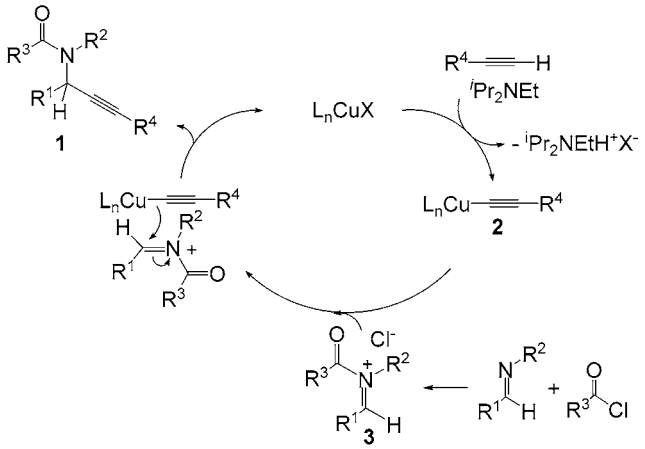
#	R^1	R^2	OR^3	R^4	%[b]
1		Et	OBn	Ph	70
2	Tol	Et	OBn	Ph	74
3		Et	OBn	Ph	82
4	Tol	Et	OBn	CO_2Me	68
5	Tol	Et	OFM[c]	Ph	88

[a] All reactions run with 0.48 mmol of imine, 0.63 mmol of chloroformate, 0.48 mmol of alkyne, 0.72 mmol of $^iPr_2NEt$, and 0.048 mmol of CuI in CH_3CN (7 mL) for 15−60 min. [b] Isolated yield. [c] FM = 9-fluorenylmethyl.

This methodology can also be extended to the use of chloroformates. This provides a facile one-pot route to convert imines into *N*-carbamate-protected secondary propargylamines (Table 2). Similar yields and diversity can be attained in this process as observed with acid chlorides. Both CBz- (entries 1−4) and FMOC-protected (entry 5) propargylamines can be generated from the appropriate chloroformate.

The exact mechanism of the copper-catalyzed process is still under investigation. Control experiments demonstrate that, in contrast to the palladium-catalyzed cross-coupling reactions, the addition of imine and acid chloride to CuI does not lead to any appreciable oxidative addition. Conversely, monitoring the reaction by ^1H NMR reveals that CuI is immediately converted to the copper acetylide **2**, and the imine quickly reacts with acid chloride to form *N*-acyliminium salt **3** (Scheme 1). While the mechanism for coupling of these two intermediates is unclear, a reasonable hypothesis would involve the attack of the copper acetylide on **3**, in direct analogy to the previously reported synthesis propargylamines via iminium salts[12,14] and alkyne addition to α-sulfonylcarbamates.[17] Alternatively, the addition of **3** to the copper center is also possible, which could subsequently reductively eliminate the product, in analogy to other cross-coupling reactions.[21,26] The nucleophilic attack on **3** is similar to that postulated in the reaction of **2** with imines themselves

Scheme 1. Postulated Mechanism for the Copper-Catalyzed Synthesis of Propargylamides



(24) α-Chloroamides are established to undergo rapid acid elimination to generate enamides (ref 25). Studies are currently underway to examine the potential use of more coordinating anions to inhibit this elimination relative to alkynylation.

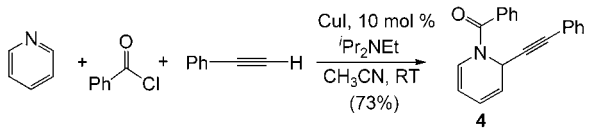
(25) Hiemstra, H.; Speckamp, W. N. In *Comprehensive Organic Synthesis*; Trost, B., Ed.; Pergamon Press: Oxford, 1991; Vol. 4, pp 1047−1082.

(26) The lack of any ligand influence on the reaction rates argues against an oxidative addition-based pathway.

or related nitrone electrophiles.[11,13,15a] In this case, the presence of the acid chloride allows not only the direct generation of propargylamides but also creates a highly reactive *N*-acyliminium salt coupling partner relative to the parent imines.[27] This is likely a factor in both the high catalytic activity observed as well as the relatively broad scope of the reaction.

As suggested by this mechanism, the activation of C═N π-bonds toward coupling by acid chlorides is not limited to imines. In particular, as shown in Scheme 2, this approach can be extended to the functionalization of nitrogen heterocycles such as pyridine. Our preliminary examination of the one-pot reaction of pyridine, benzoyl chloride, and phenylacetylene under the same conditions as those employed with imines results in the clean coupling of these three reagents to form **4** in 73% yield. This generates what is to our knowledge a unique and mild room-temperature method to directly ortho-alkynylate the pyridine core.

Scheme 2. Three-component Coupling of Pyridine, Acid Chloride, and Alkyne Catalyzed by CuI



In conclusion, we have developed a copper-catalyzed multicomponent coupling of imines, alkynes, and acid chlorides or chloroformates. This provides an efficient method to construct propargylamides and N-protected propargylamines, as well as one that can be readily diversified. Studies directed toward the control of enantioselectivity in this process, as well as the use of other transmetalating agents or C═N substrates, are currently underway.

Acknowledgment. We thank NSERC and FCAR for their financial support.

Supporting Information Available: Synthesis and spectral data for propargylamides. This material is available free of charge via the Internet at http://pubs.acs.org.

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(27) The lack of ketone products (from acetylide reaction with acid chloride) can be attributed to the fast generation of **3**, which undergoes rapid coupling (rt, 15 min) coupling with **2**.