ORGANIC LETTERS

2010
Vol. 12, No. 18
4038−4041

1,1-Dibromo-1-alkenes as Valuable Partners in the Copper-Catalyzed Direct Alkynylation of Azoles

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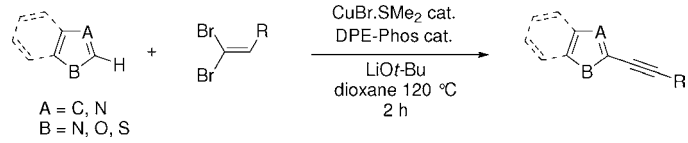
Received July 15, 2010

ABSTRACT

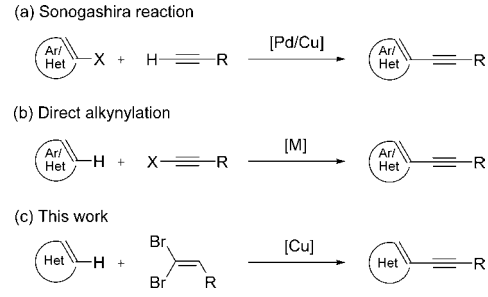


The copper-catalyzed direct alkynylation of azoles with 1,1-dibromo-1-alkenes as electrophiles is described. These easily accessible substrates are a useful addition to the field of direct alkynylations in an efficient and functional group tolerant reaction to provide a straightforward entry to diverse alkynyl heterocycles.

Acetylenes are key building blocks in organic chemistry, chemical biology, and materials science.[1] The Sonogashira cross-coupling reaction between a (hetero)aryl or alkenyl halide and a terminal alkyne has become an indispensable and powerful tool for the organic chemist to introduce such a motif.[2] An attractive and complementary strategy relies on the transition-metal-catalyzed direct C−H bond functionalization between an sp^2-hybridized (hetero)aryl carbon and an sp-hybridized carbon of an alkynyl halide. This direct alkynylation of "unreactive" C−H bonds has been rarely studied until recently, when notable advances were reported (Scheme 1).[3] Despite this remarkable interest, the use of 1,1-dibromo-1-alkenes in the direct functionalization of C−H bonds has not yet been studied (Scheme 1).

The versatility of 1,1-dihalo-1-alkenes has been exploited, notably, as alkyne equivalents in the synthesis of 1,3-diynes or internal alkynes.[4] 1,1-Dihalo-1-alkenes have also served in cross-coupling reactions with various organometallic reagents including organotin, magnesium, borane, and zinc compounds to give the corresponding trisubstituted alkenes with high stereoselectivity.[5] In addition, the *gem*-dihalovinyl moiety has become a key unit for the synthesis of various heterocycles and carbocycles through tandem catalysis.[6] More recently, 1,1-dibromo-1-alkenes proved to be reactive partners in copper-mediated couplings as shown by the synthesis of ynamides or ketene *N*,*N*-acetals.[7]

Scheme 1. General Approaches for Alkynylation



Herein, we disclose that 1,1-dibromo-1-alkenes can be employed as alkynyl equivalents in the copper-catalyzed

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(1) (a) Siemsen, P.; Livingston, R. C.; Diederich, F. *Angew. Chem., Int. Ed.* **2000**, *39*, 2632. (b) *Acetylene Chemistry*; Diederich, F., Tykwiski, R. R., Stang, P., Eds; Wiley-VCH: Weinheim, Germany, 2005.
(2) Chinchilla, R.; Nájera, C. *Chem. Rev.* **2007**, *107*, 874.

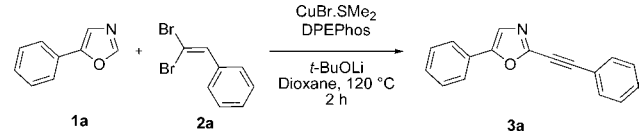
10.1021/ol1016433
Published on Web 08/24/2010

direct alkynylation of azoles, providing an efficient new route to diverse (hetero)aryl alkynes (Scheme 1).

As part of our program directed toward the development of metal-catalyzed C−H bond functionalization, we found that the copper/diphosphine duet enabled the direct alkynylation of various azoles with 1-bromoalkynes.[3j] Furthermore, we hypothesized that their direct precursors, the 1,1-bromo-1-alkenes, could serve as a reaction partner in such a process. Indeed, treatment of 5-phenyloxazole **1** with 1,1-dibromostyrene **2** in the presence of CuBr·SMe_2 (15 mol %), DPEPhos (15 mol %) as ligand, LiO*t*-Bu (4 equiv) as base in dioxane at 120 °C (Table 1, entry 1) delivered the desired product **3a** in 40% yield after 2 h but without complete conversion. Following this encouraging preliminary result, a brief optimization of the reaction conditions was performed. While no improvement in yield was obtained even after prolonged heating (Table 1, entry 2), an increase in the amount of LiO*t*-Bu (from 4 equiv) gave a positive effect, giving **3a** in 58% yield (5 equiv) and 70% yield (6 equiv) with complete conversion (Table 1, entries 3 and 4). Mixing organic and inorganic bases was detrimental to the direct alkynylation process returning starting material (Table 1, entries 5−7). The catalyst loading could be decreased down to 5 mol % without affecting the yield. However, at these low loadings, a 2:1 ratio ligand to catalyst proved to be crucial to maintain the highest yield (Table 1, entries 8−10). A brief examination of ligand structure showed no striking effect when XantPhos and BINAP were used (Table 1, entries 11 and 12). Thus, the optimum conditions were shown to be CuBr·SMe_2 (5 mol %), DPEPhos (10 mol %), and LiO*t*-Bu (6 equiv) in dioxane at 120 °C.

This optimized protocol was subsequently applied to the direct alkynylation of 5-phenyloxazole **1a** with various

Table 1. Optimization toward Direct Alkynylation of 5-Phenyloxazole[a]



entry	CuBr·SMe_2 (mol %)	DPEPhos (mol %)	LiO*t*Bu (equiv)	yield (%)[b]
1	15	15	4	40
2	15	15	4	48[c]
3	15	15	5	58
4	15	15	6	70
5	15	15	2 + 2 DBU	0
6	15	15	2 + 3 Cs_2CO_3	traces[d]
7	15	15	2 + 3 Li_2CO_3	traces[d]
8	10	10	6	71
9	5	5	6	58
10	5	10	6	69
11	5	10	6	69[e]
12	5	10	6	50[f]

[a] All reactions were performed at 0.35 M of 5-phenyloxazole **1a** (1 equiv), 2,2-dibromovinylbenzene **2a** (2 equiv), CuBr·SMe_2 (15 mol %), DPEPhos (15 mol %), LiO*t*-Bu in dioxane heated at 120 °C for 2 h. [b] Isolated yields. [c] The reaction was run overnight. [d] 2,2-Dibromovinylbenzene (1.5 equiv) was used, and the reaction was run for 24 h. [e] XantPhos was used as ligand. [f] BINAP was used as ligand.

readily accessible 1,1-dibromo-1-alkenes (Scheme 2). These building blocks are commonly prepared from the corresponding commercially available aldehydes via the Ramirez procedure.[8] Both electron-rich (Scheme 2: **3a**, **3b**, **3c**, **3d**, **3e**, **3f**) and electron-deficient (Scheme 2: **3g**, **3h**, **3i**) *gem*-dibromoolefins reacted regioselectively at the C-2 position of 5-phenyloxazole **1a** in good yields, with substitution being tolerated at each of the *ortho*, *meta*, and *para* positions. Importantly, these conditions proved to be compatible with the presence of important functional groups on the aromatic moiety such as halides (63−65%), nitro (44%), and cyano (48%). It is noteworthy that the acetal group survives these reaction conditions, providing the expected compound **3m** in a satisfactory 55% yield. In addition to the aryl group, the reaction also proceeds equally well with different *gem*-dibromoolefins including heteroaryl- and alkenyl-substituted alkenes (Scheme 2: **3j**, **3k**, **3l**). Unfortunately, these conditions were not found to be applicable to related 1,1-dibromoalkenes bearing a simple alkyl substituent. The apparent lack of reactivity for this substrate is still unclear at this stage, and investigations to overcome this issue are ongoing.

Next, the reaction scope was also investigated with respect to the heterocycles. The C-2 position of oxazoles bearing electronically different aryl/styryl groups at C-5 was alkynylated to furnish **4**, **5** and **6** in 61%, 75% and 53% yields respectively (Scheme 3). Moreover, the electron-donating dimethylamino group was tolerant of the reaction conditions

(3) (a) Kalinin, V. K.; Pashchenko, D. N.; She, F. *Mendeleev Commun.* **1992**, *2*, 60. (b) Kobayashi, K.; Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* **2002**, *124*, 8528. (c) Trofimov, B. A.; Stepanova, Z. V.; Sobenina, L. N.; Mikhaleva, A. I.; Ushakov, I. A. *Tetrahedron Lett.* **2004**, *45*, 6513. (d) Amemiya, R.; Fujii, A.; Yamaguchi, M. *Tetrahedron Lett.* **2004**, *45*, 4333. (e) Seregin, I. V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *124*, 8528. (f) Gu, Y.; Wang, X. *Tetrahedron Lett.* **2009**, *50*, 763. (g) Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250. (h) For a single example of palladium-catalyzed direct alkynylation of sidnones (34% yield), see: Rodriguez, A.; Fennessy, R.; Moran, W. *Tetrahedron Lett.* **2009**, *50*, 3942. (i) Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 4156. (j) Besselièvre, F.; Piguel, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9953. (k) Brand, J. P.; Charpentier, J.; Waser, J. *Angew. Chem., Int. Ed.* **2009**, *48*, 9346. (l) Dudnik, A. S.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2010**, *49*, 2096. (m) Kawano, T.; Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *J. Org. Chem.* **2010**, *75*, 1764. (n) Kim, S. H.; Chang, S. *Org. Lett.* **2010**, *12*, 1868.

(4) Selected examples: (a) Shen, W.; Thomas, S. A. *Org. Lett.* **2000**, *2*, 2857, and references cited therein. (b) Lera, M.; Hayes, C. J. *Org. Lett.* **2000**, *2*, 3873. (c) Chelucci, G.; Capitta, F.; Baldino, S. *Tetrahedron* **2008**, *64*, 10250. (d) Rao, M. L. N.; Jadhav, D. N.; Dasgupta, P. *Org. Lett.* **2010**, *12*, 2048.

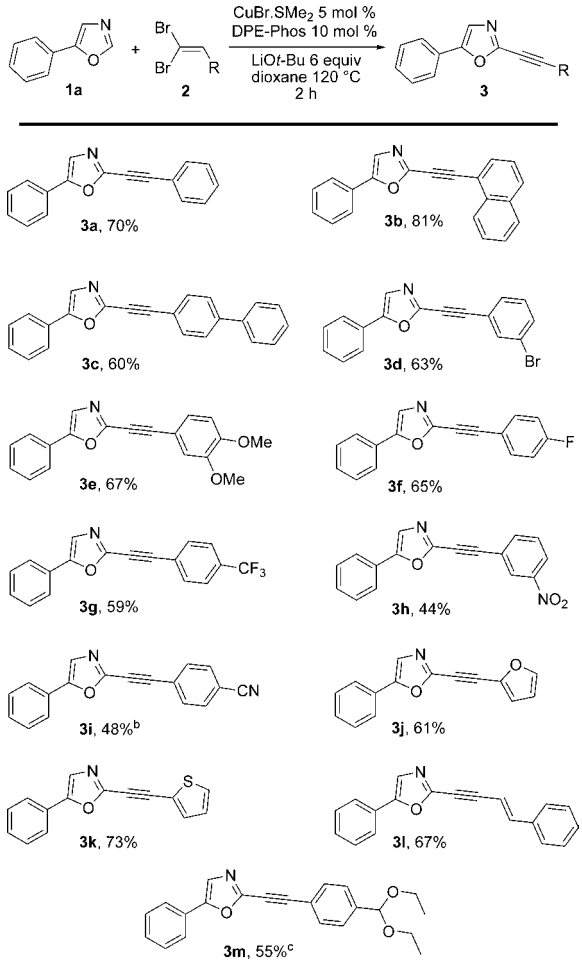
(5) Wang, J.-R.; Manabe, K. *Synthesis* **2009**, *9*, 1405, and references cited therein.

(6) (a) Bryan, C. S.; Lautens, M. *Org. Lett.* **2010**, *12*, 2754, and references cited therein. (b) Arthuis, M.; Pontikis, R.; Florent, J.-C. *Org. Lett.* **2009**, *11*, 4608. (c) Vieira, T. O.; Meaney, L. A.; Shi, Y.-L.; Alper, H. *Org. Lett.* **2008**, *10*, 4899. (d) Thielges, S.; Meddah, E.; Bisseret, P.; Eustache, J. *Tetrahedron Lett.* **2004**, *45*, 907. (e) Wang, L.; Shen, W. *Tetrahedron Lett.* **1998**, *39*, 7625.

(7) (a) Newman, S. G.; Aureggi, V.; Bryan, C. S.; Lautens, M. *Chem. Commun.* **2009**, 5236. (b) Coste, A.; Karthikeyan, G.; Couty, F.; Evano, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 4381. (c) Coste, A.; Couty, F.; Evano, G. *Org. Lett.* **2009**, *11*, 4454. (d) Yuen, J.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 653.

(8) Ramirez, F.; Desai, N. B.; Mc Kelvie, N. *J. Am. Chem. Soc.* **1962**, *84*, 1745.

Scheme 2. Scope of Direct Alkynylation of 5-Phenyloxazole with Vinyl Dibromides[a]

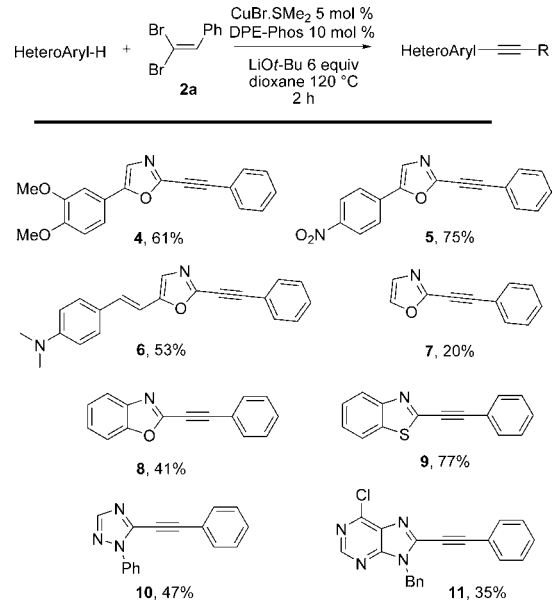


[a] Reaction conditions: 5-phenyloxazole **1a** (1 equiv), *gem*-dibromovinylbenzene **2a** (2 equiv), Li*O*t-Bu (6 equiv), dioxane (0.35 M), 120 °C for 2 h. Yields are calculated on isolated products (average of two runs). [b] *gem*-Dibromovinylbenzene (3 equiv), CuBr·SMe$_2$ (10 mol %), and DPEPhos (10 mol %) were used. [c] CuBr·SMe$_2$ (10 mol %) and DPEPhos (10 mol %) were used.

(Scheme 3: **6**). This substitution pattern along with the acetal group in compound **3m** have never been reported before in such a process. Oxazole itself was regioselectively alkynylated at the C-2 position, however only a low yield was obtained. Other heterocycles, such as benzoxazole, benzothiazole, 1,2,4-triazole and N-benzyl-6-chloropurine were also found to be suitable substrates with varying reactivities (Scheme 3: **8**, **9**, **10** and **11**).

An overview of the proposed mechanism is shown in Scheme 4. The sequence begins with the deprotonation of the oxazole by Li*O*t-Bu followed by lithium−copper transmetalation to generate a copper(I)(oxazolate) intermediate **B** as illustrated by Daugulis for the copper-catalyzed direct arylation of heterocycles.[9] Then, two hypotheses both involving the formation of a copper(III) complex **C** or **D** could be considered.[10] Path 1 involves the preliminary formation of alkynyl bromide **12** by dehydrobromination of the 1,1-dibromo-1-alkene **2**. Subsequent oxidative addition

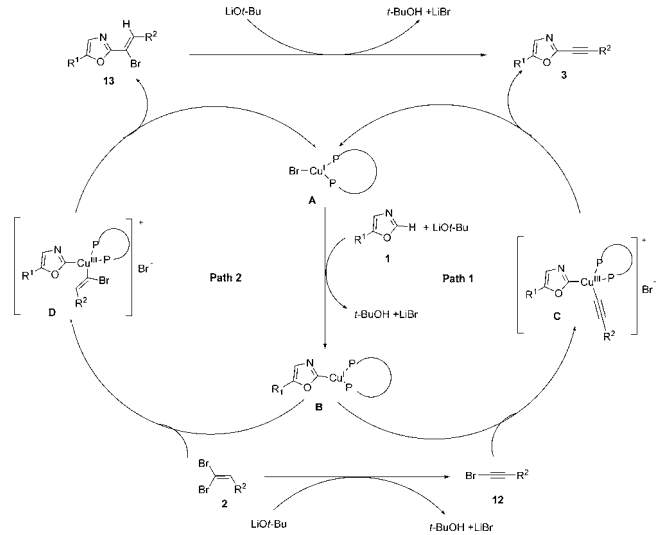
Scheme 3. Scope with Respect to the Heterocycles[a]



[a] Reaction run with 2 equiv of 2,2-dibromovinylbenzene **2a** and 1 equiv of heterocycle, CuBr·SMe$_2$ (5 mol %), DPEPhos (10 mol %), Li*O*t-Bu (6 equiv) in dioxane at 120 °C for 2 h. Yields are calculated on isolated products (average of two runs).

of the alkynyl bromide onto **B** presumably gives a four-coordinated copper(III) complex **C**. A subsequent reductive elimination would lead to the expected compound **3** and regenerate the catalytic copper(I) species **A** in the process. In path 2, the first steps would involve the direct alkenylation of azoles on the more reactive *trans* C−Br bond of the *gem*-dibromoolefin to furnish the trisubstituted alkene **13**. Dehydrobromination would then take place at the late stage to generate the expected compound **3**. However, the synthesis

Scheme 4. Mechanistic Proposal for Copper-Catalyzed Direct Alkynylation of Heterocycles with *gem*-Dibromoolefin



of 1-bromoalkynes in the presence of base is a well-known and easy transformation. Taking into account that these compounds have been identified in the crude reaction mixture and **13** was never isolated, it is reasonable to suppose that this direct alkynylation with 1,1-dibromo-1-alkenes proceeds through path 1.

In summary, we have shown that 1,1-dibromo-1-alkenes are useful new coupling partners in the direct alkynylation of various azoles under copper catalysis. The reaction is rapid, functional group tolerant, and proceeds in moderate to good yields. In this way, 1,1-dibromo-1-alkenes act as synthetic equivalents of 1-bromoalkynes, thus representing a new landmark in the field of direct alkynylation reactions.

Acknowledgment. The Institut Curie and the Agence Nationale de la Recherche are thanked for financial support.

Supporting Information Available: Experimental procedures, and copies of ^{1}H and ^{13}C for all compounds **1b**, **2c**, **2m**, **3a**−**m**, **4**, **5**, **6**, **7**, **8**, **9**, **10**, and **11**. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) Do, H.-Q.; Daugulis, O. *J. Am. Chem. Soc.* **2007**, *129*, 12404.

(10) For discussion of mechanisms involving copper(III) species, see: (a) Casitas, A.; King, A. E.; Parella, T.; Costas, M.; Stahl, S. S.; Ribas, X. *Chem. Sci.* **2010**, 326. (b) Strieter, E. R.; Bhayana, B.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 78. (c) Phipps, R. J.; Gaunt, M. J. *Science* **2009**, *323*, 1593. (d) Monnier, F.; Turtaut, F.; Duroure, L.; Taillefer, M. *Org. Lett.* **2008**, *10*, 3203. (e) Huffman, L. M.; Stahl, S. S. *J. Am. Chem. Soc.* **2008**, *130*, 9196, and references cited therein. (f) Ouali, A.; Spindler, J.-F.; Jutand, A.; Taillefer, M. *Adv. Synth. Catal.* **2007**, *349*, 1906. (g) Altman, R. A.; Koval, E. D.; Buchwald, S. L. *J. Org. Chem.* **2007**, *72*, 6190. (h) Zhang, S.-L.; Liu, L.; Fu, Y.; Guo, Q.-X. *Organometallics* **2007**, *26*, 4546. (i) Ley, S. V.; Thomas, A. W. *Angew. Chem., Int. Ed.* **2003**, *42*, 5400.