ORGANIC LETTERS

2006
Vol. 8, No. 5
879−881

Substitution of Hydroxyl Groups with Alkynyl Moieties Using Alkynylboron Dihalides: An Efficient Approach to Secondary Alkylacetylene Derivatives

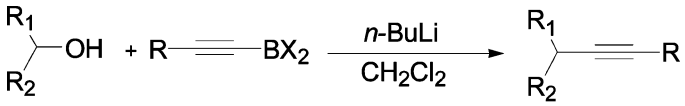
George W. Kabalka,* Min-Liang Yao, and Scott Borella

Departments of Chemistry and Radiology, The University of Tennessee, Knoxville, Tennessee 37996-1600

kabalka@utk.edu

Received December 6, 2005

ABSTRACT



R = aryl, alkyl
R_1, R_2 = aryl, vinyl, propargyl, methyl

The reaction of alkynylboron dihalides with benzylic, allylic, and propargylic alcohols provides an efficient route to internal acetylenes. Isomerization of the product alkynes does not occur under the reaction conditions.

Alkynes are important building blocks in materials science[1] and organic synthesis.[2] They are also a common structural unit in natural products and drugs.[3] Among the synthetic approaches to internal alkynes, the palladium-catalyzed Sonogashira cross-coupling reaction between terminal alkynes and aryl/alkenyl halides is widely utilized.[4] Recent modifications include the use of more efficient palladium catalysts[5] and more active alkynylmetal coupling partners (e.g., Sn,[6] Zn,[7] Mg,[8] Al,[9] and B[10]). However, the palladium-catalyzed alkynylation of allylic, benzylic, and propargylic electrophiles

* To whom all correspondence should be addressed. Phone: (865) 974-2160. Fax: (865) 974-2297.

(1) Recent reviews: (a) Höger, S. *Angew. Chem., Int. Ed.* **2005**, *44*, 3806. (b) Long, N. J.; Williams, C. K. *Angew. Chem., Int. Ed.* **2003**, *42*, 2586. (c) Pieterse, K.; Lauritsen, A.; Schenning, A. P. H. J.; Vekemans, J. A. J. M.; Meijer, E. M. *Chem. Eur. J.* **2003**, *9*, 5597. (d) Collings, J. C.; Parsons, A. C.; Porrès, L.; Beeby, A.; Batsanov, A. S.; Howard, J. A. K.; Lydon, D. P.; Low, P. J.; Fairlamb, I. J. S.; Marder, T. B. *Chem. Commun.* **2005**, 2666. (e) Hwang, G. T.; Son, H. S.; Ku, J. K.; Kim, B. H. *J. Am. Chem. Soc.* **2003**, *125*, 11241.

(2) Recent reviews: (a) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. *Angew. Chem., Int. Ed.* **2004**, *43*, 3368. (b) Bytschkov, I.; Doye, S. *Eur. J. Org. Chem.* **2003**, 935. (c) Komdo, T.; Mitsudo, T. *Chem. Rev.* **2000**, *100*, 3205. (d) Suginome, M.; Ito, Y. *Chem. Rev.* **2000**, *100*, 3221. (e) Smith, N. D.; Mancuso, J.; Lautens, M. *Chem. Rev.* **2000**, *100*, 3257.

(3) (a) *Chemistry and Biology of Naturally-Occurring Acetylenes and Related Compounds*; Lam, J., Breteler, H., Arnsaon, T., Hansen, L., Eds.; Elsevier: Amsterdam, 1988. (b) López, S.; Fernández-Trillo, F.; Castedo, L.; Saá, C. *Org. Lett.* **2003**, *5*, 3725. (c) Stütz, A.; Petranyi, G. *J. Med. Chem.* **1984**, *27*, 1539.

(4) (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467. (b) Review: Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F., Stang, P. J., Eds.; Wiley: Weinheim, 1997; 203. (c) Tykwinski, R. R. *Angew. Chem., Int. Ed.* **2003**, *42*, 1566.

(5) (a) Hierso, J.-C.; Fihri, A.; Amardeil, R.; Meunier, P.; Doucet, H.; Santelli, M.; Ivanov, V. V. *Org. Lett.* **2004**, *6*, 3473. (b) Eckhardt, M.; Fu, G. C. *J. Am. Chem. Soc.* **2003**, *125*, 13642. (c) Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729. (d) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020. (e) Böhm, V. P. W.; Herrmann, W. A. *Eur. J. Org. Chem.* **2000**, 3679. (f) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc.* **1999**, *121*, 9550.

(6) (a) Farina, V.; Krishnamurthy, V.; Scott. W. J. *Org. React.* **1997**, *50*, 1. (b) Cui, D.-M.; Hashimoto, N.; Ikeda, S.-I, Sato, Y. *J. Org. Chem.* **1995**, *60*, 5752.

(7) (a) Qian, M.; Negishi, E.-i. *Tetrahedron Lett.* **2005**, *46*, 2927. (b) Anastasia, L.; Negishi, E.-i. *Org. Lett.* **2001**, *3*, 3111.

(8) (a) Yang, L.-M.; Huang, L.-F.; Luh, T.-Y. *Org. Lett.* **2004**, *6*, 1461. (b) Negishi, E.-i.; Zhang, Y.; Cederbaum, F. E.; Webb, M. B. *J. Org. Chem.* **1986**, *51*, 4080. (c) Dang, H. P.; Linstrumelle, G. *Tetrahedron Lett.* **1978**, 191.

(9) (a) Gelman, D.; Tsvelikhovsky, D.; Molander, G. A.; Blum, J. *J. Org. Chem.* **2002**, *67*, 6287. (b) Negishi, E.-i. *Acc. Chem. Res.* **1982**, *15*, 340.

(10) (a) Molander, G. A.; Katona, B. W.; Machrouhi, F. *J. Org. Chem.* **2002**, *67*, 8416. (b) Castanet, A.-S.; Colobert, F.; Schlama, T. *Org. Lett.* **2000**, *2*, 3559. (c) Oh, C. H.; Jung, S. H. *Tetrahedron Lett.* **2000**, *41*, 8513. (d) Soderquist, J. A.; Matos, K.; Rane, A.; Ramos, J. *Tetrahedron Lett.* **1995**, *36*, 2401. (e) Fürstner, A.; Seidel, G. *Tetrahedron* **1995**, *51*, 11165.

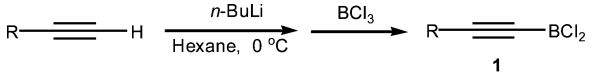
10.1021/ol052957i CCC: $33.50
Published on Web 02/04/2006

has not been well developed;[11] only a few examples have appeared in the literature.[7a,12] As a result, preparations of secondary alkylacetylene derivatives still rely on traditional methods such as substitution reactions of secondary halides or elimination reactions involving 1,2-dihalides.[13] Since these reactions often require the use of strong bases or high temperatures, in most cases the desired products are contaminated by allene byproducts that are difficult to remove.[14] Therefore, an alternative route to these important reagents would be desirable.

Our research has focused on the chemistry of boron halide derivatives for many years, and several novel reactions have been developed.[15] Very recently, we reported the substitution of hydroxyl groups with alkenyl moieties using alkenylboron dihalides.[16] The particularly appealing features of this novel reaction are the mild reaction conditions and the absence of a transition metal. A mechanistic study revealed that the reaction involves a migration of the halovinyl group (C_{sp^2}) from boron to the carbon attached to oxygen. Encouraged by these results, we postulated that an alkynyl group (C_{sp}) migration from boron to carbon might also occur. This would provide a novel route to secondary alkylacetylene derivatives from readily available alcohols. In this paper, we describe the results of our study.

Unlike alkenylboron dihalides, the chemistry of alkynylboron dihalides has not drawn much attention. Only one method is currently available to generate alkynylboron dihalides based on the boron−tin exchange reaction of boron halides with alkynylstannanes at −78 °C.[17] Considering the toxicity of tin compounds, we examined the possibility of generating alkynylboron dihalides by the sequential in situ treatment of terminal alkynes with *n*-BuLi followed by boron trichloride at 0 °C (Scheme 1).[18] Using this procedure, both

Scheme 1. Preparation of Alkynylboron Dihalides



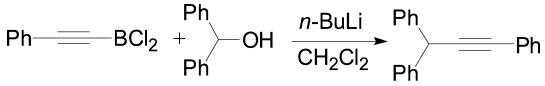
1

R = Ph (**1a**); *p*-MePh (**1b**); *o*-FPh (**1c**); *p*-MeOPh (**1d**); *n*-C_8H_{17} (**1e**)

aryl and aliphatic alkynes can be converted to the corresponding alkynylboron dihalides **1a**−**e**.

Due to its ready availability, diphenylmethanol, **2a**, was chosen as a model substrate to investigate alkynyl group migration (Scheme 2).

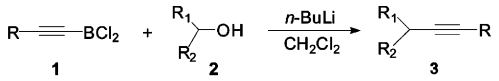
Scheme 2. Preparation of 1,3,3-Triphenyl-1-propyne



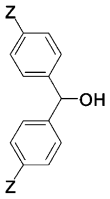
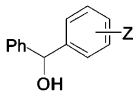
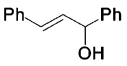
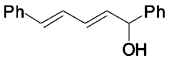
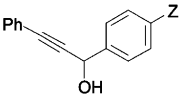
1a **2a** **3a**

Fortunately, the reaction proceeded smoothly using alkynylboron dichloride **1a** in the presence of *n*-BuLi at room temperature.[19] The desired product **3a** was isolated in 68% yield. The NMR resonances observed at 90.2 and 84.9 ppm in the ^{13}C NMR spectrum clearly demonstrate the existence of the alkynyl group. In the ^{1}H NMR, a resonance at 5.19 ppm (singlet) was observed. To evaluate the scope and limitations of the new reaction, alcohols **2a**−**j** were prepared

Table 1. Coupling of Alkynylboron Dichloride **1** with **2**[a]



1 **2** **3**

alkynylboron **1**	alcohol **2**	product **3**	yield[b] (%)
1a	 **2a:** Z = H	**3a**	68
1b	**2a:** Z = H	**3b**	64
1c	**2a:** Z = H	**3c**	76
1a	**2b:** Z = OMe	**3d**	81
1b	**2b:** Z = OMe	**3e**	77
1a	**2c:** Z = F	**3f**	74
1d	**2c:** Z = F	**3g**	57
1a	 **2d:** Z = *p*-Cl	**3h**	84
1c	**2d:** Z = *p*-Cl	**3i**	71
1a	**2e:** Z = *o*-Me	**3j**	54
1c	 **2f**	**3k**	26
1a	 **2g**	**3l**	93
1c		**3m**	86
1a	 **2h**	**3n**	71
1a	 **2i:** Z = Cl	**3o**	69
1a	**2j:** Z = Me	**3p**	77
1b	**2j:** Z = Me	**3q**	83
1e	**2j:** Z = Me	**3r**	37

[a] Reaction carried out at room temperature on a 1.5 mmol scale in dry methylene chloride (for the detailed procedure, see ref 19). [b] Yield of isolated product based on the alkynylboron dichloride (alkyne).

and subjected to the reaction conditions (Table 1). The reactions proceeded smoothly with benzylic, allylic, and

(11) (a) Negishi, E.-i.; Anastasia, L. *Chem. Rev.* **2003**, *103*, 1979.

(12) (a) Pérez, I.; Sestelo, J. P.; Sarandeses, L. A. *J. Am. Chem. Soc.* **2001**, *123*, 4155. (b) Pérez, I.; Sestelo, J. P.; Sarandeses, L. A. *Org. Lett.* **1999**, *1*, 1267.

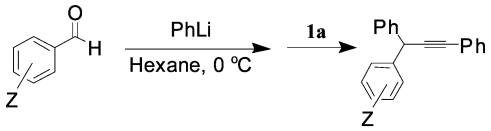
(13) (a) Brandsma, L. *Preparative Acetylenic Chemistry*; Elsevier: New York, 1988. (b) Nicholas, K. M.; Siegel, J. *J. Am. Chem. Soc.* **1985**, *107*, 4999. (c) Marcuzzi, F.; Modena, G.; Melloni, G. *J. Org. Chem.* **1982**, *47*, 4577.

(14) (a) *March's Advanced Organic Chemistry: Reactions, Mechanism, and Structure*, 5th ed.; Smith, M. B., March, J., Eds.; Wiley Interscience: New York, 2001. (b) Ma, S.; He, Q.; Zhang, X. *J. Org. Chem.* **2005**, *70*, 3336. (c) Enomoto, M.; Katsuki, T.; Yamaguchi, M. *Tetrahedron Lett.* **1986**, *27*, 4599.

propargylic alcohols and produced the desired products in good to high yields. Although alkynylation of benzylic halides has been reported,[7a,11] alkynylation of benzylic alcohols had not yet been achieved. The successful alkynylation of allylic and propargylic alcohols provides a new route to 1,4-enynes **3l**−**n** and 1,4-diynes **3o**−**r** which are suitable for further elaboration.

In recent years, much effort has been devoted to tandem reactions due to their potential utility in converting simple starting materials into relatively complex molecules in a rapid and efficient manner.[20] Therefore, the in situ generation of benzylic alkoxides from aryl aldehydes followed by treatment with an alkynylboron dihalide was also examined (Scheme 3). The reaction is quite efficient and produces the anticipated products in good yield.

Scheme 3. A Tandem Reaction to Internal Alkynes



Z = H, **3a**, 57%; Z = Cl, **3h**, 64%

In summary, we report a novel method for generating alkynylboron dichlorides and their subsequent reaction with secondary alcohols. The migration of the alkynyl group from boron to carbon occurs under very mild reaction conditions. The reaction provides an alternative route to secondary alkylacetylene derivatives from readily available secondary alcohols (the precursor of the alkoxides) and alkynes. The new procedure obviates the difficulties associated with the Pd-catalyzed alkynylation syntheses. Notably, the method successfully overcomes the isomerizations that often occur in the preparation of internal alkynes.

Acknowledgment. We thank the U.S. Department of Energy and the Robert H. Cole Foundation for support of this research. Acknowledgment is made to the donors of the Petroleum Research Fund for support of this research.

Supporting Information Available: Experimental procedures for synthesis and full characterization for compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

OL052957I

(15) (a) Kabalka, G. W.; Wu, Z.; Trotman, S. E.; Gao, X. *Org. Lett.* **2000**, *2*, 255. (b) Kabalka, G. W.; Wu, Z. *Tetrahedron Lett.* **2000**, *41*, 579. (c) Kabalka, G. W.; Wu, Z.; Ju. Y. *Tetrahedron Lett.* **2001**, *42*, 5793. (d) Kabalka, G. W.; Wu, Z.; Ju. Y. *Org. Lett.* **2002**, *4*, 1491. (e) Kabalka, G. W.; Wu, Z.; Ju. Y. *J. Organomet. Chem.* **2003**, *680* (1−2), 12.

(16) (a) Kabalka, G. W.; Yao, M.-L.; Borella, S.; Wu, Z.-Z. *Org. Lett.* **2005**, *7*, 2865. (b) Kabalka, G. W.; Yao, M.-L.; Borella, S.; Wu, Z.-Z. *Chem. Commun.* **2005**, 2492. (c) Kabalka, G. W.; Wu, Z.; Ju, Y. *Org. Lett.* **2004**, *6*, 3929.

(17) Leung, S.-W.; Singleton, D. A. *J. Org. Chem.* **1997**, *62*, 1955.

(18) A similar procedure to alkynylzinic derivatives has been reported by Negishi. See ref 7b.

(19) **Typical Experimental Procedure.** A solution of alkyne (1.5 mmol) in dry hexane (8 mL) was treated with *n*-butyllithium (1.0 mL of a 1.6 M solution in hexane) at 0 °C. After the reaction mixture was stirred at room temperature for 30 min, boron trihalide (1.5 mmol) was added. In a separate flask, the benzylic alcohol (1.6 mmol) in dry dichloromethane (8 mL) was treated with *n*-butyllithium (1.0 mL of a 1.6 M solution in hexane) at 0 °C and warmed to room temperature. After being stirred at room temperature for 30 min, this solution was transferred to the first flask and the mixture was allowed to stir overnight. Water (20 mL) was added to quench the reaction. The mixture was extracted with ethyl acetate and dried over anhydrous $MgSO_4$. The solvent was removed in vacuo and the product purified by silica gel column chromatography using hexane as an eluent to provide **3a** in 68% yield.

(20) (a) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115. (b) Parsons, P. J.; Penkett, C. S.; Shell, A. J. *Chem. Rev.* **1996**, *96*, 195.