Tetrahedron Letters 49 (2008) 7097–7099

Contents lists available at ScienceDirect

Tetrahedron Letters

journal homepage: www.elsevier.com/locate/tetlet

Highly efficient palladium-catalyzed hydrostannation of ethyl ethynyl ether

Ian P. Andrews, Ohyun Kwon *

Department of Chemistry and Biochemistry, University of California, Los Angeles, 607 Charles E. Young Drive East, Los Angeles, CA 90095-1569, USA

ARTICLE INFO

Article history:
Received 25 September 2008
Accepted 25 September 2008
Available online 1 October 2008

ABSTRACT

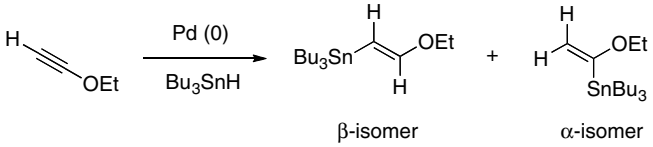
The palladium-catalyzed hydrostannation of acetylenes is widely exploited in organic synthesis as a means of forming vinyl stannanes for use in palladium-catalyzed cross-coupling reactions. Application of this methodology to ethyl ethynyl ether results in an enol ether that is challenging to isolate from the crude reaction mixture because of incompatibility with typical silica gel chromatography. Reported here is a highly efficient procedure for the palladium-catalyzed hydrostannation of ethyl ethynyl ether using 0.1% palladium(0) catalyst and 1.0 equiv of tributyltin hydride. The product obtained is a mixture of regioisomers that can be carried forward with exclusive reaction of the β-isomer. This method is highly reproducible, relative to previously reported procedures, it is more economical and involves a more facile purification procedure.

1. Introduction

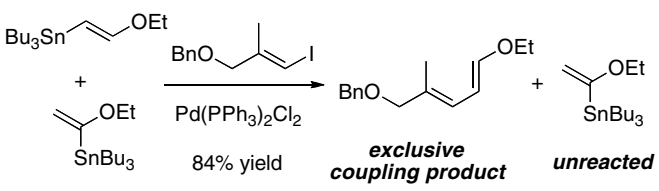
The palladium-catalyzed hydrostannation of acetylenes is a well-known and useful reaction in organic synthesis.[1] Application of this methodology to ethyl ethynyl ether[2] results in *syn* addition of tributyltin hydride across the alkyne, forming a mixture of α and β isomers of the ethyl enol ether (Scheme 1).[3]

The vinyl stannanes produced are valuable compounds for use in Stille cross-coupling reactions—for example, in the total syntheses of carazostatin and hyellazole and in our laboratory's continuing effort toward guanacastepene A.[4,5] For our purposes, coupling of (*E*)-[(4-iodo-3-methylbut-3-enyloxy)methyl]benzene with a mixture of the α and β regioisomers of the tributylstannyl enol ether proceeded without complication: only the (*E*)-tributyl(2-ethoxyvinyl)stannane coupled with the vinyl iodide (Scheme 2). This result is consistent with the much lower reactivity observed with the more sterically congested α regioisomers.[6] (*E*)-(β-Ethoxyvinyl)stannane has also been reported as a substrate for coupling with 5-bromo-2-chloro-4-aminopyrimidines to form 2-chloro-5-(2-ethoxyvinyl)-4-aminopyrimidines and to provide pyrrolopyrimidine structures after hydrolysis of the enol ether functionality and cyclization to form the pyrrole portion of the ring system.[7] We have received several requests for the detailed experimental procedure of our palladium-catalyzed hydrostannation of ethoxy acetylene; since its original appearance[5] we have significantly improved the procedure, which we report herein.

Although similar transformations of acetylenes using stannylcyanocuprates have been reported to proceed with much greater regiocontrol relative to those of palladium-catalyzed reactions,[8] this methodology provided us with poor results—that is, little or no desired product evident in the ^{1}H NMR spectrum of the crude reaction mixture—when attempted with ethoxy ethynyl ether as the substrate. Other routes offering enhanced regioselectivity include the use of 1-bromoalkynes as substrates or sterically bulkier ligands on the palladium catalyst; unfortunately, the reported reactions have not featured alkoxy-substituted alkynes.[9] Maleczka and co-workers reported that one-pot hydrostannation/Stille coupling reactions proceeded with similar regioselectivity to those of other palladium-catalyzed hydrostannations, although the majority of the examples include *tert*-alkyl-substituted terminal acetylene substrates.[10] In one reported example, however, when using a stoichiometric amount of tributyltin hydride, they obtained a 71% yield of the coupled product when the terminal acetylene



Scheme 1. The palladium-catalyzed hydrostannation of ethyl ethynyl ether.



Scheme 2. Palladium-catalyzed Stille coupling of a mixture of both vinyl stannane regioisomers.

* Corresponding author. Tel.: +1 310 267 4954; fax: +1 310 206 3722.
E-mail address: ohyun@chem.ucla.edu (O. Kwon).

0040-4039/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tetlet.2008.09.147

possessed a primary alkyl substituent. Thus, we were motivated to apply Maleczka's methodology to the hydrostannation of ethyl ethynyl ether. Because the stannanes are typically not isolated, we employed ^{1}H NMR spectroscopy to analyze the crude reaction mixture to determine the conversion of ethoxy acetylene into its hydrostannation products. Using a $CDCl_3$ solution containing maleic anhydride as the internal standard, we found that consumption of the starting material led to formation of the two vinyl stannanes in a combined yield of only 33%. We concluded that, like other hydrostannation procedures, Maleczka's procedure was not amenable to alkoxy-substituted acetylenes.

Because tetrakis(triphenylphosphine)palladium, which is typically employed as the catalyst for hydrostannation, and ethoxy ethynyl ether are both expensive commercial materials, efficient and high-yielding reactions of this type would be very desirable. An additional challenge is purification of the vinyl stannane products from the crude reaction mixture—the enol ether unit present is readily hydrolyzed under the conditions of typical silica gel chromatography. Even with more stable vinyl stannanes, some product loss is expected during column chromatography as a result of proteolytic cleavage of the tin–carbon bond.[3b] Although these compounds can be distilled from their crude reaction mixtures under high vacuum, a typical 5% catalyst loading leaves a significant mass of solid impurities from the catalyst, trapping small amounts of product and causing excessive bumping. In this Letter, however, we report a highly efficient and facile procedure for the formation and purification of this sensitive vinyl stannane in 95% isolated yield (β:α ratio, 1:0.69; ^{1}H NMR spectroscopy) from commercially available ethoxy ethynyl ether and a catalytic amount (0.1 mol %) of tetrakis(triphenylphosphine)palladium(0).

In an effort to reduce the amount of solid residue left from the catalyst in the crude reaction mixture, we used ^{1}H NMR spectroscopy to monitor the hydrostannations with varying catalyst loadings. These reactions all reached completion almost immediately at catalyst loadings as low as 0.1%, which we believe to be the lowest value reported for the palladium-catalyzed hydrostannation of any acetylene. This low loading not only makes the reaction much more economical, but it also allows for more facile distillation of the desired product from a much smaller amount of solid material. The reaction conditions employed for a hydrostannation typically call for more than 1.0 equiv of tributyltin hydride, resulting in yet another challenge in purification.[3,11] Excess tributyltin hydride reacts with the transition metal catalyst to produce the byproduct hexabutylditin, which is difficult to remove through fractional distillation.[3b] We found that reducing the amount of tributyltin hydride to 1.0 equiv had no effect on the rate of the reaction or the overall conversion of alkyne into the desired products, but it reduced the formation of hexabutylditin.

In conclusion, we believe that the procedure described herein (see Section 2) is the most facile method for the hydrostannation of ethyl ethynyl ether. This procedure is a highly efficient, high yielding, and highly reproducible, forming a mixture of (*E*)-tributyl(2-ethoxyvinyl)stannane and tributyl(1-ethoxyvinyl)stannane from commercially available ethyl ethynyl ether. Because only 0.001 equiv of tetrakis(triphenylphosphine)palladium(0) and 1.0 equiv of tributyltin hydride are required, the reaction is quite economical and the products are easily removed from the byproducts and catalyst in the crude reaction mixture.

2. Experimental

2.1. General

Tetrakis(triphenylphosphine)palladium(0) was purchased from Strem as a yellow powder and used without further purification. Tributyltin hydride was purchased from Alfa Aesar as a colorless liquid and used without further purification. Ethyl ethynyl ether was purchased from Alfa Aesar as a 50%-by-weight solution in hexanes. Immediately prior to use, the brown solution of ethyl ethynyl ether was distilled at atmospheric pressure under argon to yield a colorless solution of the alkyne in hexanes; the acetylene-to-hexanes ratio was determined through ^{1}H NMR spectroscopic analysis. Methylene chloride was distilled from calcium hydride prior to use. Reaction monitoring and determination of the regioisomeric ratios were performed through ^{1}H NMR spectroscopic analysis using a Bruker 300-MHz NMR spectrometer and samples dissolved in deuterated chloroform.

2.2. *E*-(β-Ethoxyvinyl)stannane

Tetrakis(triphenylphosphine)-palladium(0) (125 mg, 0.108 mmol, 0.001 equiv) were added to a flame-dried flask equipped with a stirrer bar and then the flask was purged with argon. Freshly distilled methylene chloride (384 mL) was then added to dissolve the catalyst. A freshly distilled solution of ethoxy acetylene (7.56 g, 108 mmol) in hexanes was then added via syringe to the stirred solution. The mixture was cooled to 0 °C and then neat tributyltin hydride (28.6 mL, 108 mmol) was added dropwise over 5 min. Immediately after the addition of tributyltin hydride, an aliquot of the reaction mixture was removed for ^{1}H NMR spectroscopic analysis. The total time that elapsed to produce the ^{1}H NMR spectrum was less than 20 min from the initial introduction of tributyltin hydride; at that point the starting acetylene was completely consumed. The solvent was evaporated under reduced pressure. The resulting dark oil was stirred and then chilled pentanes was added until no further precipitation occurred. The brown precipitate was separated through gravity filtration and the solvent evaporated under reduced pressure. The crude oil was purified through high vacuum distillation (110–115 °C at 0.25 mmHg; the α isomer had a slightly lower boiling point) yielding 37.1 g (95%) of a colorless oil. ^{1}H NMR spectroscopic analysis of the purified material revealed the presence of the two regioisomers in a 1:0.69 ratio (β:α); their signals were consistent with those reported in the literature.[8]

Acknowledgment

We thank the NIH (R01GM071779 and P41GM081282) for funding.

References and notes

1. For reviews on hydrostannation, see: (a) Leung, L. T.; Chiu, P. *Pure Appl. Chem.* **2006**, *78*, 281–285; (b) Trost, B. M.; Ball, Z. T. *Synthesis* **2005**, 853–887; (c) Smith, N. D.; Mancuso, J.; Lautens, M. *Chem. Rev.* **2000**, *100*, 3257–3283; (d) Asao, N.; Yamamoto, Y. *Bull. Chem. Soc. Jpn.* **2000**, *73*, 1071–1087; (e) Francois, G. *Main Group Metal Chem.* **1989**, *12*, 437–446. For recent examples of hydrostannation of acetylenes, see: (f) Faraoni, M. B.; Gerbino, D. C.; Podesta, J. C. *J. Organomet. Chem.* **2008**, *693*, 1877–1885; (g) Darwish, A.; Lang, A.; Kim, T.; Chong, J. M. *Org. Lett.* **2008**, *10*, 861–864; (h) Hamez, A.; Provot, O.; Brion, J.-D.; Alami, M. *J. Org. Chem.* **2007**, *72*, 3868–3874; (i) Wesquet, A. O.; Doerrenbaecher, S.; Kazmaier, U. *Synlett* **2006**, 1105–1109.
2. The Chemical Abstracts Service (CAS) database shows 17 vendors selling ethoxy acetylene in quantities ranging from several milligrams to 1 kg. On the other hand, methoxy acetylene is available only from one vendor in milligram quantity.
3. (a) Ichinose, Y.; Oda, H.; Oshima, K.; Utimoto, K. *J. Bull. Chem. Soc. Jpn.* **1987**, *60*, 3468–3470; (b) Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857–1867. For rhodium catalyzed hydrostannation of acetylenes, see: (c) Kikukawa, K.; Umekawa, H.; Wada, F.; Matsuda, T. *Chem. Lett.* **1988**, *17*, 881–884.
4. (a) Choshi, T.; Sada, T.; Fujimoto, H.; Nagayama, N.; Sugino, E.; Hibino, S. *Tetrahedron Lett.* **1996**, *37*, 2593–2596; (b) Choshi, T.; Sada, T.; Fujimoto, H.; Nagayama, C.; Sugina, E.; Hibino, S. *J. Org. Chem.* **1997**, *62*, 2535–2543.
5. Du, X.; Chu, H.; Kwon, O. *Tetrahedron Lett.* **2004**, *45*, 8843–8846.

6. Corey, E. J.; Han, X.; Stoltz, B. M. *J. Am. Chem. Soc.* **1999**, *121*, 7600–7605.
7. (a) Choi, H.; Wang, Z.; Richmond, W.; He, X.; Yang, K.; Jiang, T.; Sim, T.; Karanewsky, D.; Gu, X.; Zhou, V.; Liu, Y.; Ohmori, O.; Caldwell, J.; Gray, N.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2173–2176; (b) Choi, H.; Wang, Z.; Richmond, W.; He, X.; Yang, K.; Jiang, T.; Karanewsky, D.; Gu, X.; Zhou, V.; Liu, Y.; Che, J.; Lee, C.; Caldwell, J.; Kanazawa, T.; Umemura, I.; Matsuura, N.; Ohmori, O.; Honda, T.; Gray, N.; He, Y. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 2689–2692; (c) Moriarty, K. J.; Koblish, H. K.; Garrabrant, T.; Maisuria, J.; Khalil, E.; Ali, F.; Petrounia, I.; Crysler, C. S.; Maroney, A. C.; Johnson, D. L.; Galemmo, R. A. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5778–5783.
8. Cabezas, J. A.; Oehlschlager, A. C. *Synthesis* **1994**, 432–442.
9. (a) Boden, C. D. J.; Pattenden, G.; Tao, Y. *J. Chem. Soc., Perkin Trans. 1* **1996**, *20*, 2417–2419; (b) Darwish, A.; Lang, A.; Kim, T.; Chong, M. J. *Org. Lett.* **2008**, *10*, 861–864.
10. Lee, K.; Gallagher, W. P.; Toskey, E. A.; Chong, W.; Maleczka, R. E. *J. Organomet. Chem.* **2006**, *691*, 1462–1465.
11. Casson, S.; Kocienski, P. *Synthesis* **1993**, 1133–1140.