ORGANIC LETTERS

2000
Vol. 2, No. 13
1935−1937

An Ammonia Equivalent for the Dimethyltitanocene-Catalyzed Intermolecular Hydroamination of Alkynes

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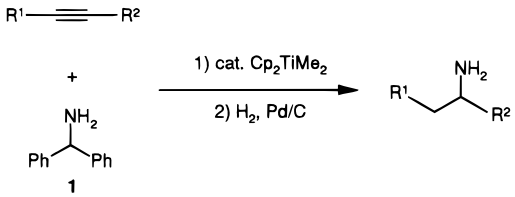
Received May 3, 2000

ABSTRACT



Commercially available α-aminodiphenylmethane 1 (benzhydrylamine) serves as a convenient ammonia equivalent in the dimethyltitanocene-catalyzed intermolecular hydroamination of alkynes. The primary formed imines can be hydrogenated and cleaved directly to the corresponding primary amines by catalytic hydrogenation using Pd/C as catalyst.

The direct addition of ammonia or amines to carbon−carbon double and triple bonds, the so-called hydroamination of alkenes and alkynes, is of fundamental interest in organic chemistry. It represents the most atom economic synthesis of amines, imines, and enamines which are important building blocks for organic products, e.g., pharmaceuticals, detergents, technical additives, and dyes. However, at the moment no general hydroamination procedure for a wide variety of substrates is known.[1,2]

Recently we reported on the dimethyltitanocene-catalyzed intermolecular hydroamination of alkynes.[3] While this procedure combined with a subsequent reduction of the initially formed imines is effective for the preparation of secondary amines, the direct use of ammonia, giving access to primary amines, has not been successful. Therefore, no simple means for the preparation of primary amines using our hydroamination strategy has yet been found. Herein we report on a procedure that uses commercially available α-aminodiphenylmethane **1** (benzhydrylamine) as a convenient ammonia equivalent in the dimethyltitanocene-catalyzed intermolecular hydroamination of alkynes.

Initial experiments to convert alkynes into primary amines using benzylamine as an ammonia equivalent in the hydroamination step followed by hydrogenation of the resulting imine have met with only limited success because benzylamine shows a very low reactivity in dimethyltitanocene-

(1) For reviews, see: (a) Taube, R. In *Applied Homogeneous Catalysis with Organometallic Compounds*; Cornils, B., Herrmann, W. A., Eds.; VCH: Weinheim, 1996; Vol. 1, pp 507−520. (b) Müller, T. E.; Beller, M. *Chem. Rev.* **1998**, *98*, 675−703. (c) Müller, T. E.; Beller, M. In *Transition Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH: Weinheim, 1998; Vol. 2, pp 316−330. (d) Haak, E.; Doye, S. *Chem. Unserer Zeit* **1999**, *33*, 296−303.

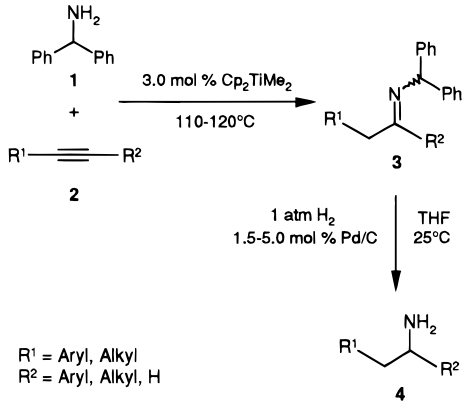
(2) For catalytic intermolecular hydroaminations of alkynes, see: (a) Barluenga, J.; Aznar, F. *Synthesis* **1977**, 195−196. (b) Barluenga, J.; Aznar, F.; Liz, R.; Rodes, R. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2732−2737. (c) Walsh, P. J.; Baranger, A. M.; Bergman, R. G. *J. Am. Chem. Soc.* **1992**, *114*, 1708−1719. (d) Baranger, A. M.; Walsh, P. J.; Bergman, R. G. *J. Am. Chem. Soc.* **1993**, *115*, 2753−2763. (e) Li, Y.; Marks, T. J. *Organometallics* **1996**, *15*, 3770−3772. (f) Haskel, A.; Straub, T.; Eisen, M. S. *Organometallics* **1996**, *15*, 3773−3775. (g) Tokunaga, M.; Eckert, M.; Wakatsuki, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3222−3225. (h) Tzalis, D.; Koradin, C.; Knochel, P. *Tetrahedron Lett.* **1999**, *40*, 6193−6195. (i) See also ref 3.

(3) Haak, E.; Bytschkov, I.; Doye, S. *Angew. Chem., Int. Ed.* **1999**, *38*, 3389−3391.

10.1021/ol006011e CCC: $19.00
Published on Web 06/01/2000

catalyzed hydroamination reactions.[3] This low reactivity which has generally been observed for primary *n*-alkylamines forced us to investigate primary *s*-alkylamines as ammonia equivalents. Among this class of compounds we found that α-aminodiphenylmethane **1** (benzhydrylamine), which offers the possibility of a reductive cleavage of the carbon−nitrogen bond,[4] serves as an ammonia equivalent in a convenient manner (Scheme 1).

Scheme 1. Formal Addition of Ammonia to Alkynes



First we found that hydroamination reactions between α-aminodiphenylmethane **1** (benzhydrylamine) and various alkynes **2** yielding the corresponding imines **3** can be realized efficiently in the presence of 3 mol % of Cp_2TiMe_2 at 110−120 °C in the absence of a solvent. The reactions are generally very clean but, however, relatively slow. For bisaryl alkynes and alkyl aryl alkynes, the reactions proceed to completion within 72 h. In contrast, reactions employing bisalkyl alkynes do not reach 100% conversion after 72 h. As shown previously,[3] for unsymmetrically substituted alkynes such as alkyl aryl alkynes and terminal alkynes the hydroamination reactions occur with high regioselectivity, forming the anti-Markovnikov products exclusively.

Further investigations showed that the crude imines **3** can be directly reduced to the desired primary amines **4** by catalytic hydrogenation under 1 atm of H_2 at 25 °C using 1.5−5 mol % of Pd/C as catalyst.[5] Table 1 shows several examples for the described hydroamination−reduction strategy.

Diphenylacetylene **2a** (entry 1) could be converted into 1,2-diphenylethylamine **4a** in 67% yield. The unsymmetrically substituted alkyl phenyl alkynes 1-phenyl-1-propyne **2b** (entry 2), 1-phenyl-1-butyne **2c** (entry 3), and 1-phenyl-1-pentyne **2d** (entry 4) were regioselectively converted into the biologically interesting phenylethylamines 2-amino-1-phenylpropane (amphetamine) **4b**, 2-amino-1-phenylbutane **4c**, and 2-amino-1-phenylpentane **4d** in 79%, 67%, and 70% yields, respectively. The use of the bisalkyl alkynes 3-hexyne **2e** (entry 5) and 4-octyne **2f** (entry 6) also gave access to the corresponding primary amines. However, the hydroamination reactions employing **2e** and **2f** did not reach 100% conversion after 72 h. Therefore, the primary amines were isolated in lower yields: 3-aminohexane **4e** was isolated in 59% yield while 4-aminooctyne **4f** was only obtained in 16% yield. Furthermore, the terminal alkyne phenylacetylene **2g** (entry 7) was converted into 2-phenylethylamine **4g**. The obtained yield was 20% when the reaction time for the hydroamination step was 72 h. It was also possible to isolate a complex mixture of amine side products from the reaction mixture. Surprisingly, the isolated yield went up to 41% when the reaction time for the hydroamination step was only 20 h. In this case the amount of the formed amine mixture decreased. However, the fact that the amount of the obtained amine side products increased with increasing reaction time for the hydroamination step indicates that the side reactions

Table 1. Synthesis of Primary Amines from Alkynes Using a Hydroamination−Reduction Strategy[5]

entry	alkyne	product	yield[a] (%)
1	Ph—≡—Ph **2a**	Ph, NH_2, Ph **4a**	67[b]
2	Ph—≡—Me **2b**	Ph, NH_2, Me **4b**	79
3	Ph—≡—Et **2c**	Ph, NH_2, Et **4c**	67[b]
4	Ph—≡—Pr **2d**	Ph, NH_2, Pr **4d**	70
5	Et—≡—Et **2e**	Et, NH_2, Et **4e**	59[b,c]
6	Pr—≡—Pr **2f**	Pr, NH_2, Pr **4f**	16
7	Ph—≡—H **2g**	Ph, NH_2 **4g**	41[b,d]

[a] Reaction conditions: (1) 1.0 equiv of amine, 1.2 equiv of alkyne, 3.0 mol % of Cp_2TiMe_2, 110 °C, 72 h; (2) 1 atm of H_2, 1.5 mol % of Pd/C, THF, 25 °C, 72 h. Reaction times have not been minimized. Yields represent isolated yields of pure compounds as judged by ^1H NMR, ^{13}C NMR, and TLC analysis. [b] 5 mol % of Pd/C was used for the reduction step. [c] 3.0 equiv of alkyne was used for the hydroamination step. [d] 20 h reaction time for the hydroamination step.

(4) Benzhydrylamines are usually cleaved more easily than benzylamines: (a) Kocienski, P. J. *Protecting Groups*; Georg Thieme Verlag: Stuttgart, New York, 1994; pp 220−227. (b) Overman, L. E.; Mendelson, L. T.; Jacobsen, E. J. *J. Am. Chem. Soc.* **1983**, *105*, 6629−6637.

(5) **General reaction procedure:** A dry Schlenk tube equipped with a Teflon stopcock was charged under an argon atmosphere with α-aminodiphenylmethane **1** (367 mg, 2.0 mmol), 1-phenyl-1-pentyne **2d** (346 mg, 2.4 mmol), and a solution of Cp_2TiMe_2 in toluene (0.18 mL, 0.33 mol/L, 0.06 mmol, 3.0 mol %). The mixture was heated to 110 °C for 72 h. The crude reaction mixture was then dissolved in THF (14 mL). Pd/C (64 mg, 3.2 mg Pd, 0.03 mmol, 1.5 mol %) was added and the mixture was stirred under 1 atm of H_2 at 25 °C for 72 h. Filtration, concentration, and purification by flash chromatography (CH_2Cl_2:CH_3OH, 10:1) afforded **4d** (230 mg, 1.41 mmol, 70%) as a colorless solid.

take place during the hydroamination step, probably lowering the yield by converting the desired product into side products. One possible explanation for this observation which is in contrast to the behavior of all other alkynes used in this study is the fact that here the imine which is initially formed in the hydroamination step is an aldimine. This aldimine can easily undergo side reactions, e.g., aldol type reactions, under the reaction conditions leading to various amine products. Therefore, the obtained yield decreases if longer reaction times are employed.

In summary, we have demonstrated the utility of employing α-aminodiphenylmethane **1** (benzhydrylamine) as a substitute for ammonia in the dimethyltitanocene-catalyzed hydroamination of alkynes. Using the presented hydroamination−reduction strategy, alkynes can be easily converted into primary amines. However, the obtained overall yield for the described reaction sequence strongly depends on the structure of the employed alkyne. While bisaryl alkynes and alkyl aryl alkynes react smoothly under the reaction conditions, bisalkyl alkynes and terminal alkynes give lower yields.

Acknowledgment. We thank Prof. Winterfeldt for his generous support of our research. We are grateful to the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for financial support and to Bayer AG for providing chemicals.

Supporting Information Available: Characterization data for compounds **4a**−**4g**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL006011E