# 1-(Trimethylsilyl)benzotriazole-Assisted Addition of Grignard Reagents to Imines: A Versatile Approach to Aliphatic Secondary Amines

Alan R. Katritzky,* Qingmei Hong, and Zhijun Yang

*Center for Heterocyclic Compounds, Department of Chemistry, University of Florida, Gainesville, Florida 32611-7200*

*Received August 29, 1994 (Revised Manuscript Received November 1, 1994®)*

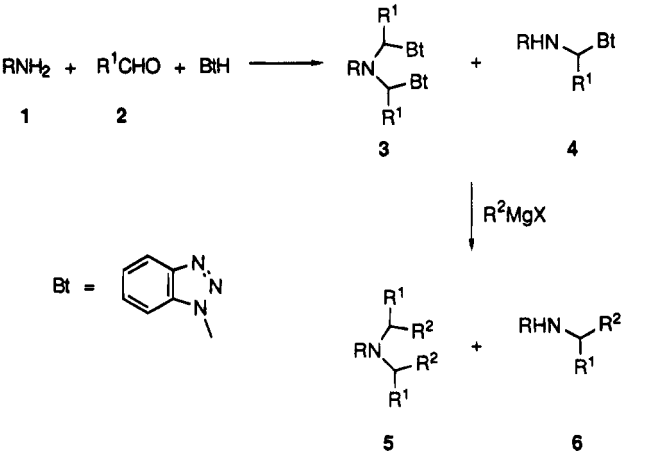
*Summary:* 1-(Trimethylsilyl)benzotriazole-assisted Grignard addition to imines is described.

Attempted reactions of imines which contain α-hydrogens with Grignard reagents generally fail to give acceptable yields of secondary amines by simple addition because of the poor electrophilicity of the imine carbon and competing loss of the α-proton.[1-3] Some organolithiums do add to certain types of imines, but the yields are generally low for the same reasons.[3-6]

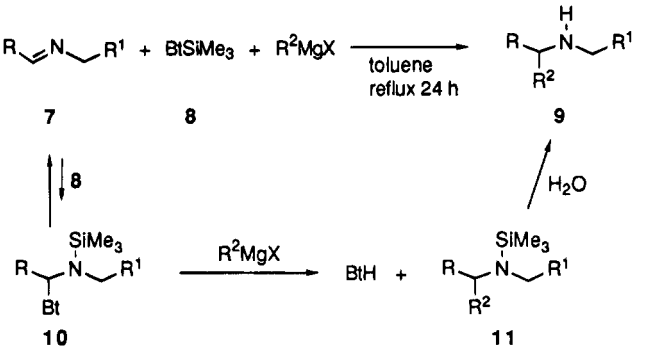
To circumvent these problems, a number of methods have been developed.[7-11] The strategy most commonly employed has involved activation of the imine carbon to nucleophilic attack by coordination of a Lewis acid to the nitrogen lone pair.[8,10,11] While this treatment enhances the electrophilicity of the imine carbon, the acidity of the protons α to N and C is also increased, which may facilitate unwanted enamine or azomethine formation. The presence of other Lewis basic centers in the starting substrate further complicates the reaction. The combined use of organocuprates (generally prepared *in situ* from Grignard reagents and CuI) and Lewis acids (mostly $BF_3$) has been reported by several groups, and many alkyl groups have been efficiently introduced (yields 47–85%),[7] although lower yields (17–56%) were reported in two cases.[10,12] More recently, Brook *et al.* reported the use of trimethylsilyl triflate (TMSOTf) in facilitating the addition of Grignard and organolithium reagents to aromatic aldehyde imines, but apparently no imines containing hydrogen α to C were investigated.[9]

Conversion of aliphatic primary amines to the more functionalized secondary amines is a challenging and important problem in organic synthesis, particularly in industry. Direct alkylation often affords mixtures of amines and is rarely useful synthetically. Reduction of imines generally requires acidic conditions (*e.g.*, $NaCNBH_3$/HCl) and lacks the versatility of functionality provided by Grignard addition. Work in this laboratory has demonstrated the use of benzotriazole as a synthetic auxiliary in the transformation of secondary amines to the corresponding tertiary amines.[13] A typical procedure generally involves Mannich condensation of benzotriazole with an aldehyde and an amine followed by displacement of the benzotriazolyl group by Grignard reagents. However, this method was much less successful when applied to the similar conversion of aliphatic primary amines to the corresponding secondary amines because the Mannich reaction of the former with an aldehyde and benzotriazole often led to mixtures of mono- and double-condensation products[14] (Scheme 1).

**Scheme 1**




**Scheme 2**




We later found that this type of condensation could be controlled to give the monoadduct when carried out in either ether–water or ether at room temperature; however, the reactions were limited to the use of formaldehyde and generally to sterically hindered aliphatic primary amines.[15] Our efforts to develop an efficient method for the conversion of aliphatic primary amines to the corresponding secondary amines have now demonstrated that 1-(trimethylsilyl)benzotriazole (**8**) efficiently facilitates the addition of both alkyl and aryl Grignard reagents to imines **7** (Scheme 2). The mechanism is believed to involve initial addition of 1-(trimethylsilyl)benzotriazole to the imine followed by displace-

® Abstract published in *Advance ACS Abstracts,* December 1, 1994.

(1) Thies, H.; Schonenberger, H. *Chem. Ber.* **1956**, *89*, 1918.
(2) Stork, G.; Dowd, S. R. *J. Am. Chem. Soc.* **1963**, *85*, 2178.
(3) Layer, R. W. *Chem. Rev.* **1963**, *63*, 489.
(4) Huet, J. *Bull. Soc. Chim. Fr.* **1964**, 952.
(5) Pattison, I.; Wade, K.; Wyatt, B. K. *J. Chem. Soc. A* **1968**, 837.
(6) Scully, F. E., Jr. *J. Org. Chem.* **1980**, *45*, 1515.
(7) Wada, M.; Sakurai, Y.; Akiba, K. *Tetrahedron Lett.* **1984**, *25*, 1079.
(8) Colvin, E. W.; McGarry, D. G. *J. Chem. Soc., Chem. Commun.* **1985**, 539.
(9) Brook, M. A.; Jahangir *Synth. Commun.* **1988**, *18*, 893.
(10) Cainelli, G.; Giacomini, D.; Panunzio, M.; Zarantonello, P. *Tetrahedron Lett.* **1992**, *33*, 7783.
(11) Giammaruco, M.; Taddei, M.; Ulivi, P. *Tetrahedron Lett.* **1993**, *34*, 3635.
(12) Ukaji, Y.; Watai, T.; Sumi, T.; Fujisawa, T. *Chem. Lett.* **1991**, 1555.
(13) Katritzky, A. R.; Rachwal, S.; Hitchings, G. J. *Tetradedron* **1991**, *47*, 2683.
(14) Katritzky, A. R.; Yannakopoulou, K.; Lue, P.; Rasala, D.; Urogdi, L. *J. Chem. Soc., Perkin Trans. 1* **1989**, 225.
(15) Katritzky, A. R.; Noble, G.; Pilarski, B.; Harris, P. *Chem. Ber.* **1990**, *123*, 1443.

0022-3263/94/1959-7947$04.50/0 

**Table 1. Addition of Grignard Reagents to Imines To Give Secondary Amines 9a–j**

| compd | R | $R^1$ | $R^2$ | yield (%) |
|---|---|---|---|---|
| **9a** | *i*-Pr | $(CH_2)_6CH_3$ | Ph | 78 |
| **9b** | *i*-Pr | $(CH_2)_6CH_3$ | $PhCH_2$ | 65 |
| **9c** | *i*-Pr | $(CH_2)_6CH_3$ | *n*-Bu | 76 |
| **9d** | *i*-Pr | $(CH_2)_6CH_3$ | Me | 60 |
| **9e** | *i*-Pr | $PhCH_2$ | Ph | 73 |
| **9f** | *i*-Pr | $PhCH_2$ | Me | 69 |
| **9g** | $CH_3(CH_2)_2$ | Ph | Ph | 70 |
| **9h** | $CH_3(CH_2)_2$ | Ph | *n*-Bu | 61 |
| **9i** | 4-$MeC_6H_4$ | $(CH_2)_6CH_3$ | Ph | 93 |
| **9j** | 4-$MeC_6H_4$ | $(CH_2)_6CH_3$ | Me | 72 |

ment of the benzotriazolyl group with Grignard reagents. The addition step must be reversible as indicated by the fact that heating **7** and **8** in the absence of Grignard reagents gave only small amounts of the addition product **10** (NMR). Comparative experiments in which we attempted to react **7** with a Grignard in the absence of 1-(trimethylsilyl)benzotriazole resulted in recovery of most of the starting material **7**.

In a typical procedure, equimolar amounts of 1-(trimethylsilyl)benzotriazole and the appropriate imine were dissolved in dry toluene and alkyl or aryl Grignard reagents (2 equiv) added. The mixture was gently refluxed for 24 h, quenched with saturated aqueous $NH_4Cl$, and extracted with diethyl ether. The pure secondary amines **9** (*cf.* Table 1) were obtained after column chromatography in yields of 60–93%.

Alternatively, the imines need not be isolated as exemplified by a one-pot preparation of *N*-(2-methyl-1-phenylpropyl)octylamine (**9a**). Thus, equimolar isobutyraldehyde and octylamine were stirred at room temperature for 30 min followed by the addition of 2 equiv of $BtSiMe_3$. The mixture was refluxed for 8 h in toluene and PhMgBr added. The mixture was heated at reflux for an additional 24 h to afford **9a** in a yield of 85%.

This method has several advantages, compared with other literature procedures, for the transformation of primary aliphatic amines to secondary amines. 1-(Trimethylsilyl)benzotriazole is readily prepared by heating equimolar quantities of benzotriazole and bis(trimethylsilyl)amine ($HN(SiMe_3)_2$) followed by distillation.[16] It is neither appreciably acidic nor basic, and therefore, side effects, such as those caused by the use of Lewis acids, are minimized. The reaction appears to be quite general, and imines possessing hydrogens α to both C and N react readily with Grignard reagents to give the corresponding secondary amines. This method, complementing our work previously reported,[15] is shown to be particularly useful for the preparation of less sterically hindered aliphatic secondary amines.

**Acknowledgment.** We thank Professor N. de Kimpe and Dr. C. Stevens for helpful discussions.

**Supplementary Material Available:** General procedures and characterization data for **9a–j** (3 pages). This material is contained in libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(16) Katritzky, A. R.; Zhang, G.-F.; Pernak, J.; Fan, W.-Q. *Heterocycles* **1993**, *36*, 1253.