SYNLETT
Spotlight 258Lithium Aluminum Hydride:
A Powerful Reducing Agent

Compiled by Srinivasarao Yaragorla

This feature focuses on a reagent chosen by a postgraduate, highlighting the uses and preparation of the reagent in current research

Srinivasarao Yaragorla was born in Sattupally, Andhra Pradesh, India in 1981, and received his Masters degree in 2003 from the University of Hyderabad. After qualifying in a CSIR-JRF exam in 2003, he started his Ph.D. studies under the supervision of Dr. S. Chandrasekhar, Deputy Director, Indian Institute of Chemical Technology, India. His research interests include asymmetric total synthesis of bioactive natural products, and medicinal chemistry.

Organic Chemistry Division-I, Indian Institute of Chemical Technology, Hyderabad 500007, India
Fax +91(40)27160512; E-mail: syaragorla@gmail.com

Introduction

Lithium aluminum hydride (LiAlH_4) is a powerful reducing agent used in organic synthesis¹ and is commonly abbreviated as LAH. It is more powerful than the related reagent sodium borohydride because of the relatively weaker Al–H bond compared to the B–H bond. It reduces a vast number of functional groups. For example, it converts esters,^{2a,b} carboxylic acids^{2c} and carbonyl compounds^{2d} into the corresponding alcohols; α,β -unsaturated ketones are reduced to allylic alcohols.^{2e} When epoxides are reduced using LAH, the reagent attacks the less hindered end of the epoxide, usually producing a secondary or tertiary alcohol. Epoxycyclohexanes are reduced to give axial alcohols preferentially.^{2f} Using LAH, amines can be prepared by the reduction of amides,^{2g,h} oximes,²ⁱ nitriles, nitro compounds or alkyl azides. LAH does not

reduce simple alkenes, arenes, or alkynes; but alkynes can be reduced if an alcohol group is nearby.^{2j}

Figure 1

Preparation

Treatment of lithium hydride with an ethereal solution of AlCl_3 produces the new ether-soluble compound, LAH.³ Addition of further quantities of AlCl_3 yields a mild reducing agent, aluminum hydride (AlH_3).⁴

Figure 2

Abstracts

(A) Stereoselective reduction

Various *syn*-1,3-diols were prepared conveniently by reduction of β -alkoxy ketones with LiI and LAH (*syn/anti* selectivity up to >99:1). Here the coordination of LiI gives rise to a *syn*-selective reducing agent as a consequence of the intervention of a Li^+ -containing six-membered chelation.⁵

(B) Reductive removal of a tosylated hydroxy group/epoxide formation/epoxide opening

LAH is also employed in a highly chemo- and regioselective reduction of 2-tosyloxy esters, followed by epoxide formation via an $\text{S}_{\text{N}}2$ mechanism and reductive opening of the epoxide.⁶

(C) *Enantioselective reduction of ketones by modified LAH*

Highly enantioselective reduction of ketones by chiral-diol modified LAH was successfully demonstrated, with good yields and high ee.⁷

(D) *Synthesis of amines*

LAH is a powerful reducing agent, it reduces azide and nitro functionalities into the corresponding amines in a one-pot process.⁸

(E) *Reduction of amides*

LAH reduces both cyclic and acyclic amides to the corresponding amines.⁹

(F) *Epoxide ring opening*

LAH attacks the epoxide at the less hindered side and produces the alcohols.¹⁰

(G) *Reduction of lactones*

LAH reduces lactones to the corresponding diols.¹¹

(H) *Formation of cyclopropane derivatives*

A homoallylic mesylate, when subjected to LAH, provided the cyclopropane derivative through homoallylic π -participation.¹²

References

- (1) Brown, H. C. *Org. React.* **1951**, 6, 469.
- (2) (a) Reetz, M. T.; Drewes, M. W.; Schwickardi, R. *Org. Synth., Coll. Vol. X* **2004**, 256. (b) Oi, R.; Sharpless, K. B. *Org. Synth., Coll. Vol. IX* **1998**, 251. (c) Oi, R.; Sharpless, K. B. *Org. Synth.* **1996**, 73, 1. (d) Koppenhoefer, B.; Schurig, V. *Org. Synth., Coll. Vol. VIII* **1993**, 434. (e) Barnier, J. P.; Champion, J.; Conia, J. M. *Org. Synth., Coll. Vol. VII* **1990**, 129. (f) Elphimoff-Felkin, I.; Sarda, P. *Org. Synth., Coll. Vol. VI* **1988**, 769. (g) Rickborn, B.; Quartucci, J. J. *Org. Chem.* **1984**, 29, 3185. (h) Seebach, D.; Kalinowski, H.-O.; Langer, W.; Crass, G.; Wilka, E.-M. *Org. Synth., Coll. Vol. VII* **1990**, 41. (i) Park, C. H.; Simmons, H. E. *Org. Synth., Coll. Vol. VI* **1988**, 382. (j) Chen, Y. K.; Jeon, S.-J.; Walsh, P. J.; Nugent, W. A. *Org. Synth.* **2005**, 82, 87. (k) Wender, P. A.; Holt, D. A.; Sieburth, S. M. c. N. *Org. Synth., Coll. Vol. VII* **1990**, 456.
- (3) Finholt, A. E.; Bond, A. C.; Schlesinger, H. I. *J. Am. Chem. Soc.* **1947**, 69, 1199.
- (4) Lopinti, K. *Synlett* **2005**, 2265; Spotlight No. 134.
- (5) Ghosh, A. K.; Lei, H. *J. Org. Chem.* **2002**, 67, 8783.
- (6) Chandrasekhar, S.; Rambabu, C.; Prakash, S. J. *Tetrahedron Lett.* **2006**, 46, 1213.
- (7) Ren, Y.; Tian, X.; Sun, K.; Xu, J.; Xu, X.; Lu, S. *Tetrahedron Lett.* **2006**, 47, 463.
- (8) Chandrasekhar, S.; Reddy, N. R.; Rao, Y. S. *Tetrahedron* **2006**, 62, 12098.
- (9) Kouklovsky, C.; Hoang, C. T.; Nguyen, V. H.; Alezra, V. *J. Org. Chem.* **2008**, 73, 1162.
- (10) Chapelon, A. S.; Moraleda, D.; Rodriguez, R.; Ollivier, C.; Santelli, M. *Tetrahedron* **2007**, 63, 11511.
- (11) Grieco, P. A.; Takigawa, T.; Schillinger, W. J. *J. Org. Chem.* **1980**, 45, 2247.
- (12) Pan, L.-R.; Tokoroyama, T. *Tetrahedron Lett.* **1992**, 33, 1473.