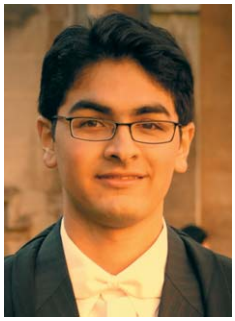
SYNLETT
Spotlight 312

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

Sodium Bis(methoxyethoxy)-aluminium Hydride



Compiled by Akshat Rathi

Akshat Rathi was born in Nashik, Maharashtra, India in 1987. He received his B.Tech. in Pharmaceutical Chemistry & Technology from the Institute of Chemical Technology (formerly UDCT), Mumbai. During his undergraduate degree, he was a research associate under Prof. S. D. Samant at Mumbai and also a visiting scholar at the University of Sheffield under the supervision of Prof. Iain Coldham. His undergraduate thesis, under Prof. M. S. Degani, involved work on the synthesis of novel systemic biological markers. At present, he is working towards his M.Sc. by Research in Organic Chemistry at the University of Oxford, under the tutelage of Prof. T. J. Donohoe. His current research project involves studies towards the synthesis of microsclerodermin F.

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Introduction

Sodium bis(methoxyethoxy)aluminium hydride (Red-Al®) is a versatile reducing agent which was developed by Vit and co-workers in 1968.[1]

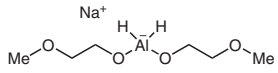
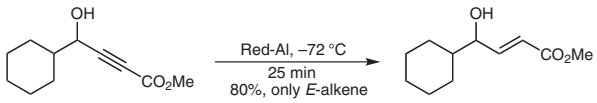


Figure 1

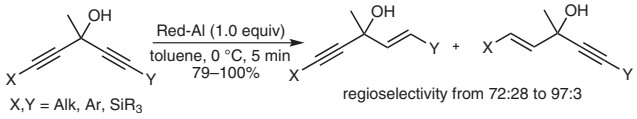
Red-Al® exhibits similar reactivity to lithium aluminium hydride but is significantly less sensitive towards air and has higher solubility in aromatic solvents and ethers. In addition, the reactions can be performed at temperatures of up to 200 °C.[2] The general mechanism of reduction using Red-Al® involves an initial reaction with an alcohol, formation of hydrogen, and subsequent hydride transfer in an intramolecular fashion. In the absence of such a moiety, the hydride reduction via a mechanism akin to lithium aluminium hydride can be envisaged. The reagent has been used towards the synthesis of many natural products.[3] Some less conventional uses involve the cleavage of benzyl ethers of vicinal methoxy-containing compounds.[4]

Abstracts

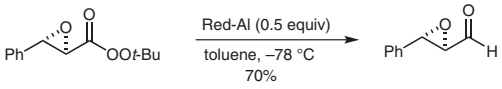
(A) Koide et al. reported the use of $NaBH_4$ or Red-Al® to achieve the reduction of propargylic alcohols to allylic alcohols. They demonstrated that Red-Al® gave only *E* alkenes whereas $NaBH_4$ gave *E*/*Z* mixtures. Superior yields were obtained with Red-Al® compared to $NaBH_4$ and fewer equivalents were required. It has also been shown that the metalated intermediates can be intercepted by an electrophile, thus allowing derivatization of the alkene in a single operation.[5]



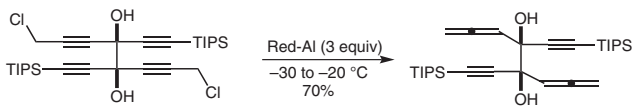
(B) Igawa and Tomooka reported the regioselective reduction of a bisalkyne to an *E* alkene. Following the preferential order of reactivity TPS > Ph ~ TBDPS > TIPS ~ TMS >> Alk, Red-Al gave regioselectivities from 72:28 to 97:3 and 79–100% yields. Other hydride reagents were reported to be less selective than Red-Al®.[6]



(C) Shibasaki et al. recently reported the use of Red-Al® in the reduction of α,β-epoxy peroxy esters to aldehydes in high yields. In this interesting transformation, the reduction of such an ester could be achieved without epoxide opening.[7]



(D) En route to the synthesis of dicyclopenta[*a*,*e*]pentalenes, Cao et al. successfully utilized Red-Al® in the reduction of a tetrayne to the corresponding bisallene–bisalkyne under high dilution conditions. Several reducing reagents including $LiAlH_4$ proved unsuccessful prior to achieving satisfactory results with Red-Al®. The reduction presumably occurs by formation of an aluminum complex of the propargylic alcohol and subsequent delivery of hydride in an S_N2' fashion.[8]



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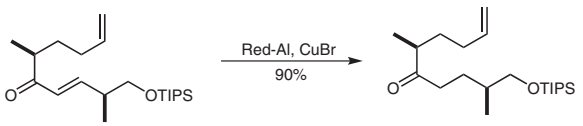
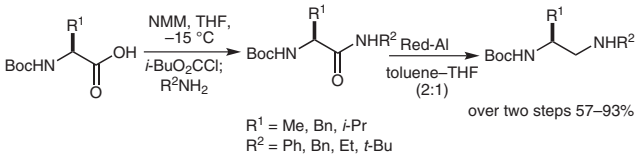
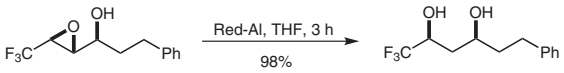
(E) Ghosh et al.[9] used Red-Al® successfully in combination with a copper salt to reduce α,β-unsaturated ketones to saturated ketones. It is believed the reaction proceeds via the formation of a copper hydride species. In the absence of copper salts only the carbonyl is reduced and the olefin remains intact.[10]



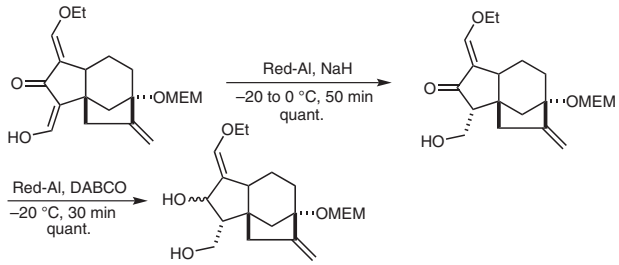
(F) Voight et al.[11] used Red-Al® for the efficient preparation of chiral diamines via selective reduction of *N*-Boc-protected amino acid derived secondary amides. The reactions proceeded with minimal overreduction or cyclic urea formation. Furthermore, no epimerization was observed during the reduction. The methodology was also extended to selective reduction of di- and tripeptides in excellent yields.



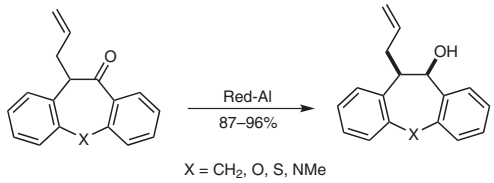
(G) The use of Red-Al for the selective opening of 2,3-epoxy alcohols has been one of the earliest reported uses.[12] While studying the Payne rearrangement Yamazaki et al. reported the use of Red-Al® for the regioselective opening of an epoxy alcohol to furnish a 1,3-diol.[13]



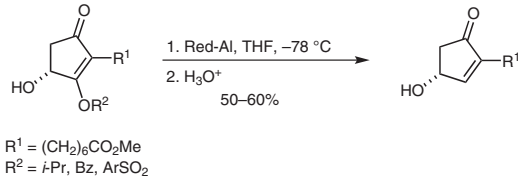
(H) Corey et al. reported the transformation shown; the regioselectivity of reduction could be controlled by the addition of a base. Other hydride reagents, such as $NaBH_4$, $LiBH_4$, L-selectride, and 9-BBN-H were unsuccessful. The first step gave a single stereoisomer and both steps gave quantitative yields.[14]



(I) Towards the synthesis of serotonin antagonists, Cid et al. used Red-Al® for stereoselective carbonyl reduction in the molecule; the *cis*-alcohols were prepared with excellent diastereoselectivities and yields.[15]



(J) In a short synthesis towards prostaglandin E_1 Sih et al. reduced the alkoxy substituent from the ring with 50–60% yields.[16]



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