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Reactions of a novel modified Red-Al reducing agent with selected organic compounds containing representative functional groups and chemoselective reduction

Ji Yeon Park, Won Kyu Shin, Ashok Kumar Jaladi, Duk Keun An *

Department of Chemistry, Kangwon National University, and Institute for Molecular Science and Fusion Technology, Chunchon 200-701, Republic of Korea

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ABSTRACT

A new modified Red-Al reagent prepared from commercially available 1,1,1,3,3,3-hexamethyldisilazane and sodium bis(2-methoxyethoxy)aluminumhydride (Red-Al) is reported for the selective reduction of carbonyl compounds containing representative functional groups. Moreover, this novel reagent is superior for the chemoselective reduction of aldehydes and ketones to the corresponding alcohols in excellent yields under mild reaction conditions. Moreover, aldehydes can be reduced selectively in the presence of ketones with similar reactivity.

Introduction

Preparation of alcohols by the reduction of carbonyl compounds is one of the most important chemical transformations in organic synthesis. For this purpose, diverse reagents have been developed in the past decades; among them, $LiAlH_4$ and $NaBH_4$ are the commonly used reducing agents.[1,2] The selective (chemo, region, and stereo) reduction of functional groups in the presence of other reducible groups is highly desired in modern synthetic approaches.[3] $NaBH_4$ is a convenient, mild, and selective reducing agent for aldehydes, ketones, and acyl chlorides.[4] Reducing agents derived from $NaBH_4$ have been widely investigated and provide quantitative yields and higher selectivities.[5–8] However, the reactions are limited to protic solvents such as methanol and ethanol. Recently, a resin-based reduction system ($NaBH_4$/DOWEX) was developed for the convenient reduction of carbonyl compounds in a nonprotic solvent such as THF, but the reaction was limited to aldehydes and ketones only.[9]

Further, the reduction of aldehydes and ketones by the Meerwein–Ponndorf–Verley (MPV) reduction[10] method using a metal alkoxide catalyst is well known. However, practical MPV reductions suffer from some drawbacks such as a longer reaction time, and reversible reactions.[11,12] $LiAlH_4$ is a powerful reducing agent; it can reduce all organic functional groups. Hence, it is difficult to use $LiAlH_4$ for the selective reduction of multifunctional groups. Unlike the $NaBH_4$ series of reducing agents, the selective reduction of functional groups using Al reducing agents in nonalcoholic solvents such as THF and ether has not been well studied. However, considerable efforts have been made for partial reductions.[13–15]

1,1,1,3,3,3-Hexamethyldisilazane (HMDS) is a bulky organosilane compound, usually used for the trimethylsilylation of alcohols, amines, and thiols. Further it is a precursor for well-known non-nucleophilic bases such as LiHMDS, NaHMDS, and KHMDS.

In continuation of our research on the development of novel reducing agents, derived from commercially available reducing agents such as DIBALH[16] or Red-Al[15] and experience in the modification of Red-Al with secondary amines for the partial reduction of carbonyl compounds, herein, we wish to report the modification of Red-Al with commercially available bulky secondary amine HMDS (Scheme 1).

Results and discussion

The reaction of Red-Al and HMDS was monitored by gas buret experiment by measuring the hydrogen gas evolution using (Fig. 1).

* Corresponding author.
E-mail address: dkan@kangwon.ac.kr (D.K. An).

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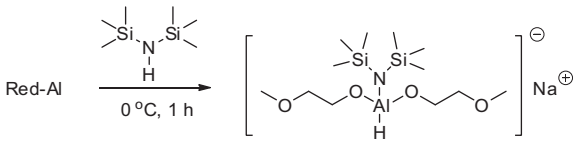


Scheme 1. Synthesis of a new modified Red-Al reagent.

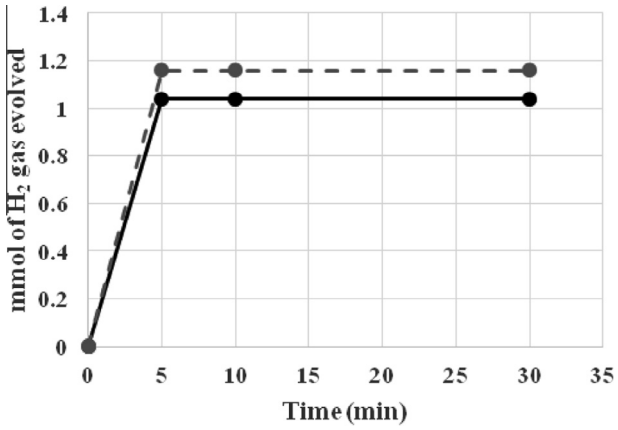
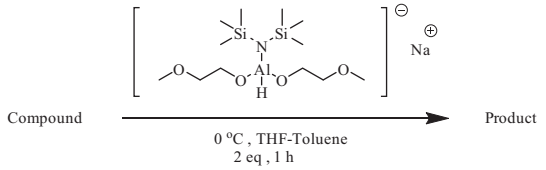
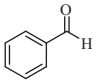
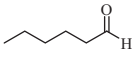
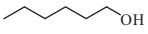
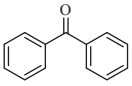
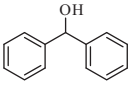
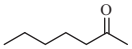
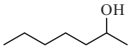


Figure 1. Measurement of hydrogen gas evolution: solid line indicates the evolution of hydrogen gas from 1 mmol of amine (HMDS) by reacting with 1 mmol of Red-Al. Dotted line indicates the evolution of hydrogen gas from 2 mmol of amine by reacting with 1 mmol of Red-Al.

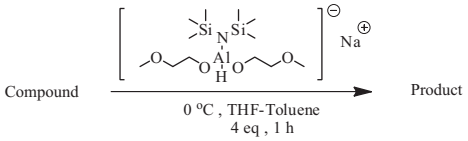
Table 1
Reaction of representative aldehydes and ketones with new modified Red-Al

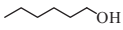
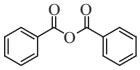
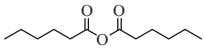
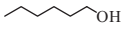
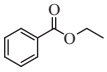
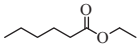
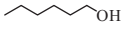
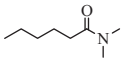
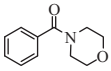
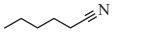
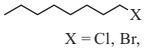


Entry	Compound	Product	Yield[a] (%)
1			>99
2			>99
3			>99
4			>99
5			>99
6			>99
7			>99

[a] Yields were determined by GC.

Table 2
Reactions of representative organic compounds with new modified Red-Al



Entry	Compound	Product	Yield[a] (%)
1			92
2			76
3			89
4			>99
5			4
6			7
7		No reaction	
8		No reaction	
9		No reaction	
10		No reaction	
11		No reaction	
12	 X = Cl, Br, I	No reaction	
13		No reaction	

[a] Yields were determined by GC.

As shown in Figure 1, the gas buret experiment shows that only one hydrogen atom of Red-Al participated in that reaction with HMDS. Therefore, 1 mmol of H_2 gas was evolved in the reaction of 1 mmol of amine (HMDS) with 1 mmol of Red-Al, whereas, the reaction of 2 mmol of HMDS with 1 mmol of Red-Al resulted in 1 mmol of H_2 gas evolution rather than 2 mmol. Therefore, this indicates that no other byproducts were generated in the preparation of new modified Red-Al reagent.

After 5 min of hydrogen gas evolution, the reaction was terminated. To evaluate the reactivity of novel Red-Al reagent, representative aldehydes and ketones were first treated with 2 equiv of reducing agent in THF at 0 °C; quantitative conversion to the corresponding alcohol was observed at 1 h (Table 1).

The reactions of aldehydes such as aromatic and aliphatic aldehydes afforded the corresponding primary alcohols (entries 1 and 2 in Table 1). Similarly, irrespective of the nature of ketones, the reaction of aromatic ketones such as acetophenone and benzophenone, aliphatic ketones such as 2-heptanone, and cyclic ketones such as cyclohexanone produced the corresponding alcohols in quantitative yields (entries 3–6 in Table 1). The reaction of α,β-unsaturated compound cyclohexenone afforded 1,2-reduction rather than 1,4-reduction (entry 7 in Table 1).

Moreover, the reaction of acyl chlorides and anhydrides with this new reagent smoothly afforded the corresponding alcohols.