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



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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.

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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, LiAlH₄ and NaBH₄ 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 NaBH₄ is a convenient, mild, and selective reducing agent for aldehydes, ketones, and acyl chlorides.⁴ Reducing agents derived from NaBH₄ 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 (NaBH₄/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) reduction¹⁰ method using a metal alkoxide catalyst is well known. However, practical MPV reductions suffer from some drawbacks such as a longer reaction

* Corresponding author. E-mail address: dkan@kangwon.ac.kr (D.K. An). time, and reversible reactions.^{11,12} LiAlH₄ is a powerful reducing agent; it can reduce all organic functional groups. Hence, it is difficult to use LiAlH₄ for the selective reduction of multifunctional groups. Unlike the NaBH₄ 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 DIBALH¹⁶ or Red-Al¹⁵ 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).





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.

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



| Entry | Compound | Product | Yield ^a (%) |
|-------|----------|----------|------------------------|
| 1 | O H | ОН | >99 |
| 2 | O H | ОН | >99 |
| 3 | | OH | >99 |
| 4 | | ОН | >99 |
| 5 | | OH | >99 |
| 6 | | OH OH | >99 |
| 7 | | ОН | >99 |

^a Yields were determined by GC.

Table 2

Reactions of representative organic compounds with new modified Red-Al





^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.

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Chemoselective reduction of aldehydes in the presence of various organic compounds using new modified Red-Al

| | | Compound + H R H A B | $\frac{\left[\begin{array}{c} \begin{array}{c} \stackrel{I}{\scriptstyle{>}} \stackrel{I}} \stackrel{I}{\scriptstyle{>}} \stackrel{I} \stackrel{I}{\scriptstyle{>}} \stackrel$ | $ \begin{bmatrix} \ominus & \\ &$ | t | |
|-------|--------------------|------------------------|---|--|--------------------------------------|-------------------------------------|
| Entry | Compound | l | Product C | Equiv | Yield of C ^a (%) | Recovery of A ^a (%) |
| | A | В | | | | |
| 1 | ∼∼∼ ⁰ H | © ⁰ H | ОГОН | 1.1 1.5 | 51 68 | 46 33 |
| 2 | CI | | | 1.1 | 60 | 76 |
| 3 | | | | 1.1 1.5 | 32 50 | 8 0 |
| 4 | | | | 1.1 1.5 | >99 ^b >99 ^b | >99 ^b 77 ^b |
| 5 | | | | 1.1 1.5 | 90 90 | 90 99 |
| 6 | | | | 1.1 1.5 2.0 | 99 >99 >99 | 98 >99 >99 |
| 7 | | | | 1.1 1.5 | >99 89 | >99 >99 |
| 8 | O N I | | | 1.1 1.5 | >99 97 | 99 91 |
| 9 | N N | | | 1.1 1.5 | 96 >99 | >99 90 |
| 10 | | | | 1.1 1.5 | >99 >99 | >99 98 |
| 11 | ~~~ ⁿ | 0 | | 1.1 1.5 | 98 >99 | >99 >99 |
| 12 | $\sim\sim$ | | ~~~ _{ОН} | 1.1 1.5 | >99 ^L 90 | 96 ^L 56 |

^a Yields were determined by GC.

^b Yields were determined by NMR.

^c Reaction was carried out at -78 °C.

However, esters showed very poor reactivity (entries 5 and 6 in Table 2), 50% conversion even after 6 h. Amides and nitriles did not produce the corresponding alcohols (entries 7–11 in Table 2). Similarly, the novel Red-Al reagent was not suitable for dehalogenation and epoxide ring opening (entries 12 and 13 in Table 2).

The bulky nature of the modified Red-Al did not allow the partial reduction of esters to the corresponding aldehydes. Thus, the modified Red-Al is a functional group-selective reducing agent for aldehydes, ketones, acyl chlorides, and anhydrides. The chemoselectivity was further investigated by the reaction of a mixture of reactants using 1.1 equiv and 1.5 equiv of the modified Red-Al reagent.

As shown in Table 3, benzaldehyde was reduced in the presence of other functional groups such as acyl chloride, ketone, ester, amide, and nitrile. Similarly, an aldehyde was reduced almost quantitatively in the presence of other functional groups except acyl chloride which might be due to similar reactivity.

Next, the selective reduction of a ketone was carried out in the presence of other functional groups such as acyl chloride, ester, amide, and nitrile. The ketone was reduced quantitatively in the presence of other functional groups. Acid chlorides produced the corresponding carboxylic acids because of their unstable nature under acidic workup conditions (entries 1 and 2 in Table 4). The results are summarized in Table 4.

Finally, the chemoselectivity of the modified Red-Al reagent for multifunctionalized compounds was investigated under the optimized conditions. The results clearly showed that the aldehyde group was reduced in the presence of a ketone in the same compound, thus affording the corresponding primary alcohol in 83% yield (entry 1 in Table 5). Moreover, the aldehyde or ketone was reduced in the presence of an ester in the same compound, thus affording the corresponding primary or secondary alcohol in excellent yields, respectively (entries 2-4 in Table 5). In the case of a compound containing an α -hydrogen, the reaction did not proceed because of the formation of an enolate through the deprotonation of α -hydrogen before the reduction (entry 5 in Table 5). The reduction of an α,β -unsaturated compound yielded a mixture of products (entry 6 in Table 5). In the case of 4-oxopentanoate, the corresponding lactone was produced by reduction followed by in situ cyclization in 86% yield (entry 7 in Table 5).

In summary a new modified Red-Al reagent was prepared by the reaction of commercially HMDS with Red-Al. This novel reagent provides selective functional group reduction in excellent-to-quantitative yields under mild reaction conditions. The experimental results show that the new modified Red-Al reagent has the potential for the chemoselective reduction of aldehydes and ketones to the corresponding alcohols in a rapid and efficient

Chemoselective reduction of ketones in the presence of various organic compounds using new modified Red-Al

| | | Compound + R A B | $\frac{\left[\begin{array}{c} \begin{array}{c} \begin{array}{c} \begin{array}{c} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \begin{array}{c} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \begin{array}{c} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \begin{array}{c} \\ \end{array} \\ \begin{array}{c} \end{array} \\ \begin{array}{c} \end{array} \\ \begin{array}{c} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \end{array} \\ \begin{array}{c} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \end{array} \\ \begin{array}{c} \\ \end{array} \\ \end{array} \\ \end{array} \\ \end{array} \\ \begin{array}{c} \\ \end{array} \\ $ | √0√ Na Toluene | Product C | |
|-------|---|---------------------|---|----------------------|------------------------------------|---------------------------------------|
| Entry | Comp | oound | Product C | Equiv | Yield of C ^a (%) | Recovery of A ^a (%) |
| | A | В | | | | |
| 1 | CI | | OH | 1.1 1.5 | 50 66 | 37 0 |
| 2 | ° CI | Ť | Ť | 1.1 1.5 | >99 99 | 0 0 |
| 3 | | | | 1.1 1.5 2.0 | >99 90 91 | 99 99 98 |
| 4 | | | | 1.1 1.5 | >99 >99 | >99 >99 |
| 5 | O N I | | | 1.1 1.5 | >99 >99 | 91 90 |
| 6 | | | | 1.1 1.5 | >99 >99 | >99 >99 |
| 7 | | | | 1.1 1.5 | >99 >99 | 89 93 |
| 8 | ∧ √ ^N | | | 1.1 1.5 | >99 >99 | >99 >99 |
| 9 | $\sim \sim $ | | | 1.1 1.5 | 98 96 | 93 >99 |
| 10 | | | | 1.1 1.5 | 95 >99 | 98 >99 |
| 11 | ∧ √ ^N | | | 1.1 1.5 | 92 >99 | >99 >99 |

^a Yields were determined by GC.

manner. Moreover, aldehydes can be reduced selectively in the presence of ketones with similar reactivity.

Experimental

General

All the glassware was dried thoroughly in an oven, assembled hot, and cooled under a stream of dry nitrogen prior to use. All the reactions and manipulation of air- and moisture-sensitive materials were carried out using the standard techniques for handling air-sensitive materials. All the chemicals were commercial reagents of the highest purity and further purified by standard methods before use. THF was dried over sodium-benzophenone and distilled before use. GC analyses were performed using a Yonglin (Anyang-si, South Korea), Acme 6000 M FID chromatograph using an HP-5 (5%-diphenyl-95%-dimethylsiloxane copolymer, 30 m) capillary column. All the GC yields were determined using a mixture of naphthalene as the internal standard and an authentic sample of the product.

Preparation of new modified Red-Al

A dry and argon-flushed flask was equipped with a magnetic stirring bar and a septum; then HMDS (5.4 mL, 55 mmol) and 80 mL THF were added. After cooling to 0 °C, Red-Al (14.3 mL, 3.5 M in toluene, 50 mmol) was added dropwise and stirred for 1 h at the same temperature, generating a colorless homogeneous solution. The concentration of the modified Red-Al solution in THF/toluene was measured gasometrically by the hydrolysis of an aliquot of the solution with aqueous 1 N HCl at 0 °C.

Representative procedure for the chemoselective reduction of multifunctionalized compounds with new modified Red-Al

A dry and argon-flushed flask, equipped with a magnetic stirring bar and septum, was charged with 4-acetylbenzaldehyde (1.0 mmol) and THF (10 mL). After cooling to 0 °C, the modified Red-Al (0.5 M, 2.2 mL in THF) was added dropwise and the mixture was stirred for 1 h at 0 °C. The reaction was quenched with 1 N aqueous HCl (10 mL) and the product was extracted with diethyl ether (10 mL). The organic layer was dried over anhydrous

Chemoselective reduction of multifunctionalized compounds with new modified Red-Al





^a Isolated yields.

magnesium sulfate, the solvent was removed under reduced pressure and the crude residue was purified by column chromatography (SiO₂, ethyl acetate/hexane, 1:5 v/v) to affording the desired alcohol (123 mg, 83% yield).

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