

Partial Reduction of Esters to Aldehydes Using a Novel Modified Red-Al Reducing Agent

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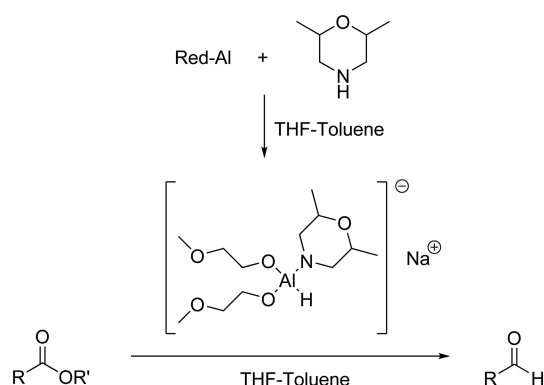
Key Words : Red-Al, *cis*-2,6-Dimethyl morpholine, Partial reduction, Ester, Aldehyde

Aldehydes are valuable building blocks and reactive intermediates in organic synthesis. The general and classical syntheses of aldehydes from esters involve reduction-oxidation and partial reduction using efficient partial reducing agents. Obviously, one-step partial reduction methods are more useful than two-step reduction-oxidation methods owing to their simplicity, and generality in organic synthesis.

Therefore, the partial reduction of esters to aldehydes without over-reduction to alcohols is useful for the synthesis of aldehydes, and a large number of reducing agents for this purpose have been reported.¹ Among them, the most popular partial reducing agent is diisobutylaluminum hydride (DIBALH)^{1a} even though this agent provides moderate yields (48–88%) and requires a very low temperature (−78 °C). Further, several substituted metal hydrides such as lithium tri-*t*-butoxyaluminum hydride (LTBA),^{1b} bis(4-methyl-1-piperazinyl)aluminum hydride,^{1c} and sodium diethylpiperidinoaluminum hydride (SDPA)^{1d,e} have been utilized for the partial reduction of esters. However, these agents suffer from low product yields, and cannot be used to achieve the partial reduction of both aliphatic and aromatic esters in similar yields.

Recently, we reported that lithium diisobutyl-*t*-butoxyaluminum hydride (LDBBA)^{1g} and sodium diisobutyl-*t*-butoxyaluminum hydride (SDBBA),^{1h} the alkoxy derivatives of DIBALH, could be employed as new partial reducing agents for the partial reduction of various esters to the corresponding aldehydes. In particular, LDBBA, which is now commercially available from Aldrich, was effective for the partial reduction of isopropyl esters to the corresponding aldehydes in most cases, whereas SDBBA was effective for the partial reduction of methyl and ethyl esters to the corresponding aldehydes with good yields at 0 °C.

As a part of our research program is directed towards the discovery of new and more useful partial reducing agents to improve the yield (compared to existing reducing agents) of aldehydes from ester, we very recently found a very effective and new modified Red-Al (sodium bis[2-methoxyethoxy]aluminum hydride) reducing agent for the synthesis of aldehydes from esters in very good to excellent yields. Red-Al derivatives of secondary amines (*e.g.*, morpholine, *N*-methylpiperazine, or pyrrolidine) can be used for the partial reduction of esters or diesters.² Among them, pyrrolidine-



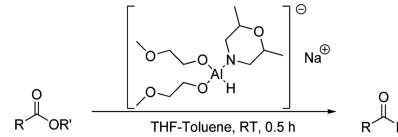
Scheme 1. Synthesis of aldehydes from esters using new modified Red-Al reagent.

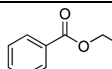
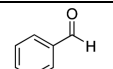
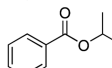
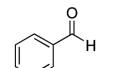
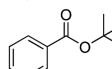
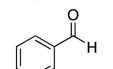
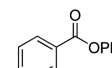
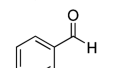
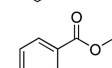
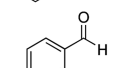
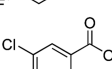
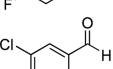
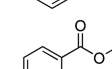
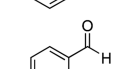
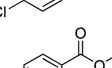
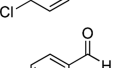
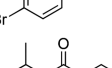
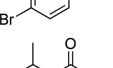
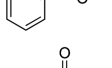
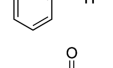
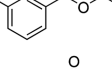
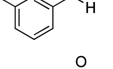
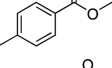
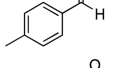
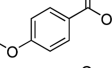
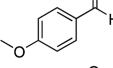
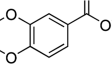
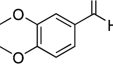
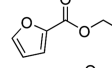
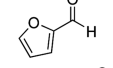
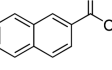
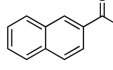
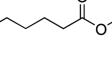
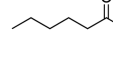
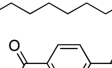
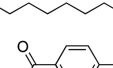
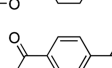
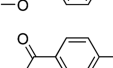
modified Red-Al was the most effective partial reducing agent for monoesters when potassium *t*-butoxide was added to the reaction to suppress the formation of by-products. However, compared to the previously reported pyrrolidine-modified Red-Al, the new modified Red-Al reducing agent synthesized from the reaction of Red-Al with *cis*-2,6-dimethyl morpholine improved the yield of aldehydes from esters without any by-products except small amount of corresponding alcohols in the absence of any additives at room temperature (Scheme 1).

After the reaction conditions were optimized through the reaction of an ester with the new modified Red-Al reagent, the partial reduction of representative esters to the corresponding aldehydes were carried out. The results are summarized in Table 1.

As shown in Table 1, various alkoxy benzoate was efficiently reduced to benzaldehyde in 97–99% yield (entry 1–4). Most esters containing electron-withdrawing substituents such as ethyl 4-fluorobenzoate, methyl 3-chlorobenzoate, and ethyl 4-chlorobenzoate, and the esters containing electron-donating substituents such as ethyl 2-toluate, ethyl 3-toluate, ethyl 4-toluate, ethyl 4-methoxybenzoate and ethyl 3,4-dimethoxybenzoate were readily reduced to the corresponding aldehydes in 83–99% yield (entries 5–8 and 9–13).

Among these, the reduction of ethyl 4-methoxybenzoate and ethyl 3,4-dimethoxybenzoate required more amounts of hydride than the other esters. These results may be attributed

Table 1. Synthesis of aldehydes from representative esters using new modified Red-Al reducing agent^a


Entry	Ester	Product	Yield (%) ^b
1			98
2			99
3			99 ^c
4			97
5			98
6			98
7			98
8			69
9			83
10			99
11			97
12			96 ^d
13			98 ^d
14			97
15			99
16			89
17			88
18			93 ^e
19			94 ^f

^aEster:Modified Red-Al=1:2. ^bYields were determined by GC. ^cEster:Modified Red-Al=1:3 and reacted for 1 h. ^dEster:Modified Red-Al=1:2.5. ^eEster:Modified Red-Al=1:1.2. ^fEster:Modified Red-Al=1:3.

to the strong electron-donating effect of the methoxy groups. The reduction of ethyl 4-bromobenzoate gave lower yields (entry 8) of the corresponding aldehyde compared to other aromatic esters due to the formation of a metal-halogen exchange by-product. The reduction of other aromatic esters such as ethyl 2-furoate, a heterocyclic aromatic ester and ethyl 2-naphthalate, a polyaromatic ester gave the corresponding aldehydes in 97% and 99% yields, respectively (entries 14-15). Aliphatic esters gave slightly lower yields of the corresponding aldehyde (88-89%) compared to the aromatic esters under the same reaction conditions (entries 16-17). Also, in the case of aromatic diester produced mono- and dialdehyde according to the amount of hydride (entries 18-19).

In conclusion, we have developed a convenient alternative method for the synthesis of aldehydes from both aromatic and aliphatic esters in very good to excellent yields in the absence of any additives using a modified Red-Al that was easily prepared by reacting commercially available Red-Al with *cis*-2,6-dimethyl morpholine. The advantages of the present methodology are as follows: (i) simple preparation procedure of the reducing agent, (ii) improved product yields, (iii) convenient reaction temperature, and (iv) short reaction times. Therefore, the new reagent has great potential to be a useful alternative partial reducing agent for the synthesis of aldehydes from esters in organic synthesis.

Experimental

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

Preparation of New Reducing Reagent (*cis*-2,6-Dimethyl Morpholine-Modified Red-Al). A dry and argon-flushed flask, equipped with a magnetic stirring bar and a septum, was charged with *cis*-2,6-dimethylmorpholine (6.81 mL, 55 mmol) and 79 mL THF. 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 same temperature to give a colorless homogeneous solution. The concentration of *cis*-2,6-dimethylmorpholine-modified Red-Al solution in THF-toluene was measured gasometrically by hydrolysis of an aliquot of the solution with a hydrolyzing of aqueous 1 N HCl at 0 °C.

Partial Reduction of Esters to Corresponding Aldehydes. The following experimental procedure for the partial reduction of ethyl benzoate to benzaldehyde is representative. A dry and argon-flushed flask, equipped with a magnetic

stirring bar and a septum, was charged with ethyl benzoate (0.07 mL, 0.5 mmol) and THF (5 mL). After cooling to 0 °C, *cis*-2,6-dimethylmorpholine-modified Red-Al (2.5 mL, 0.4 M 1.0 mmol) was added dropwise and the mixture was stirred for 30 min at the room temperature. The reaction was stopped aqueous 1 N HCl (5 mL) and the product was extracted with diethyl ether (10 mL). The ether layer was dried over anhydrous magnesium sulfate. GC analysis showed a 98% yield of benzaldehyde. All products in Table 1 were confirmed through comparison with GC data of authentic sample.

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