

genase. It is strongly believed that the mechanism of alcohol dehydrogenase reaction is hydride-like rather than radical mechanism.

Since cyclopropylmethanol derivatives such as (1) were known as latent inhibitors of horse liver alcohol dehydrogenase,¹⁰ it seemed to be interesting to know whether or not such highly strained compounds as (2) and (3) inhibited the enzyme. Compound (2) or (3) was incubated with horse liver alcohol dehydrogenase and the activity was checked following the exactly same procedure as reported previously.¹⁰ Surprisingly, the enzyme was not inhibited by (2) or (3) at all although their K_m and k_{cat} values determined by Lineweaver-Burk plot were similar to (1).¹¹ Therefore, the steric hindrance exerted by methyl substitutions on the cyclopropane ring effectively prevents the enzymic residue from attacking the ring in S_N2 fashion, Compound (2) and (3) are expected to be useful as the mechanistic probe avoiding complications resulting from the nucleophilic ring-opening in alcohol dehydrogenase reactions as well as other enzymatic reactions.

Acknowledgement. This research was supported by Academic Foundation from Chonnam National University and the Korea Science and Engineering Foundation. Author is indebted to Miss S. Kim for running kinetic experiments.

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6. A stirred solution of 2.0 g of (5) in 500 ml of pentane was irradiated through quartz for 4 hr with Hanovia lamp. After the starting material disappeared based on NMR, the pentane was evaporated to produce 1.4 g of (4) (83%). Compound (4) (1.0 g) was dissolved in 30 ml ether and 10 equivalents of lithium aluminium hydride was added. The reaction mixture was stirred for 30 min and standard workup produced 0.7 g of (3) (90%).
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8. The authentic sample of compound (I) was prepared by oxidation of (2) by pyridiniumchlorochromate.
9. NMR spectrum of compound (II) (250 MHz, $CDCl_3$): 9.21 (s, 1H, -CHO), 1.48 (d, 5.0 Hz, 1H, cyclopropyl proton), 1.30 (s, 3H, -CH₃), 1.20 (s, 3H, -CH₃), 1.08 (s, 3H, -CH₃), 0.82 (d, 5.0 Hz, 1H, cyclopropyl proton).
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11. K_m values and k_{cat} values of (1), (2), (3) were 6.89×10^{-5} M, 70.4×10^{-5} M, 140×10^{-5} M, 4.24 S^{-1} , 7.79 S^{-1} , 10.03 S^{-1} respectively.

Selective Reduction by Lithium Bis- or Tris(di-alkylamino)aluminum Hydrides. VI. One-Pot Conversion of Primary Carboxamides into Aldehydes via Stepwise Treatment with Diisobutylaluminum Hydride and Lithium Tris(diethylamino)aluminum Hydride¹

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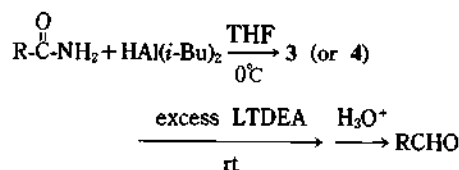
Received December 19, 1991

In the previous communications², we reported a new methodology for direct transformation of both aliphatic and aromatic primary carboxamides to the corresponding aldehydes by utilizing lithium tris(diethylamino)aluminum hydride (LTDEA) and lithium tripiperidinoaluminum hydride (LT-PDA). These results led us to think over the reaction pathway. Consequently, we found an alternative simple method for such transformation. Herein, we now report this reduction of primary carboxamides to the corresponding aldehydes by using diisobutylaluminum hydride (DIBAH) and LTDEA.

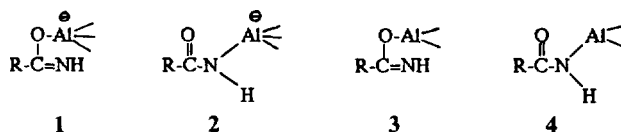
One of the most important features to be considered in this reaction seems to be the reaction intermediates which are formed after the hydrogen evolution from the reaction of primary amide and reagent (Scheme 1). In cases where LTDEA is utilized, the intermediate would be 1 or 2 and where DIBAH is used, the intermediate would be 3 or 4.

When compared 1 with 3 (or, 2 with 4), we could expect that the intermediate without negative charge on aluminum would be more favorable to reduction through the more efficient electron-withdrawing effect.

Therefore, we added 1 equiv of DIBAH to the solution of carboxamides to form the intermediate 3 (or 4) at 0°C³, and treated it with excess LTDEA at room temperature consecutively in the hope of resulting in the rate and yield enhancement (Eq 1).



The system reduces aliphatic primary carboxamides readily at room temperature to provide the corresponding aldehydes in yields of 50-70%, as shown in Table 1. The yields of aldehydes appear to be varying with the structure of



Scheme 1

Table 1. Yields of Aldehydes in the Reduction of Primary Carboxamides Through Treatment of N-Diisobutylaluminumcarboxamides with Lithium Tris(diethylamino)aluminum Hydride in Tetrahydrofuran at Room Temperature^a

| Class | Amide | Reaction time (h) | Yield of aldehyde (%) ^b |
|---------------------|-------------------------|-------------------|------------------------------------|
| Aliphatic | acetamide | 3.0 | 52 |
| | 2-chloroacetamide | 3.0 | 56 |
| | trimethylacetamide | 6.0 | 71 |
| | <i>n</i> -butyramide | 3.0 | 60 |
| | isobutyramide | 3.0 | 64 |
| | methacrylamide | 3.0 | 50 |
| | caproamide | 3.0 | 62 (68) ^c |
| | octadecaneamide | 6.0 | 70 (72) ^c |
| | cyclohexane-carboxamide | 3.0 | 63 |
| | Aromatic | benzamide | 3.0 |
| <i>o</i> -toluamide | | 1.0 | 77 |
| 4-methoxybenzamide | | 1.0 | 74 |
| 2-ethoxybenzamide | | 1.0 | 70 |
| 2-chlorobenzamide | | 3.0 | 71 |
| 2-nitrobenzamide | | 1.0 | 36 |
| nicotinamide | | 1.0 | 62 |

^a3 Equiv of LTDEA used. ^bAnalyzed with (2,4-dinitrophenyl)hydrazine. ^c2 Equiv of LTDEA utilized. ^dat 0°C.

amides examined. Aromatic carboxamides are also readily converted into the corresponding aldehydes in yields more than 70%, except for nitrobenzamides. The nitro group itself appears to be reduced readily. Derivatives containing alkyl, alkoxy or halogeno group are readily accommodated. Nicotinamide is also converted into the corresponding aldehyde in a yield of 62%.

In general, the yields of aldehydes obtained from this system appear to be similar to those obtained from LTDEA itself², however the rate of reduction in this procedure is much faster. Thus, this system requires the reaction time of 1-3 h, but LTDEA itself requires 6-12 h both at room temperature.

The following procedure for the reduction of *o*-toluamide is illustrative. An oven-dried, 50-ml flask, fitted with a side arm and a bent adaptor connected to a mercury bubbler, was charged with 3.3 ml of 1.5 M solution of *o*-toluamide (0.677 g, 5.0 mmol) in THF. The solution was cooled to 0°C and 2.0 ml of DIBAH-THF solution (2.5 M, 5.0 mmol) was injected dropwise. After the hydrogen evolution was ceased, the reaction mixture was warmed to room temperature and 11 ml of LTDEA-THF solution (1.4 M, 1.5 mmol) was added. The mixture was stirred for 1 h at room temperature. Analysis of the reaction mixture with (2,4-dinitrophenyl)hydrazine showed a yield of 77%.

Acknowledgement. The authors thank the Organic Chemistry Research Center-KOSEF for the financial support.

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Mechanism of Aldehyde Synthesis from Ester by Sodium Diethylpiperidinoaluminum

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Received January 20, 1992

Among several metal hydrides, which are reported to be useful for aldehyde synthesis from carboxylic acid esters¹⁻⁵, diisobutylaluminum hydride (DIBAH) has been most generally utilized for the aldehyde synthesis from esters. However the very low temperature (-70°C) required for the DIBAH reduction is still a considerable handicap, especially for larger samples. Recently we have reported that sodium diethylpiperidinoaluminum (SDPA) prepared from equimolar sodium diethyldihydroaluminum (SDDA) and piperidine in THF-toluene, is an excellent reagent for the aldehyde synthesis⁶. Thus we could obtain aromatic aldehydes quantitatively even though the yields of aliphatic aldehydes varied depending on the structure (60-90%). In the hope of clarifying the mechanism of the reaction, we studied the reaction of ethyl benzoate with 5 different *sec*-amine derivatives of SDDA (Table 1). As shown in Table 1, the yield of benzaldehyde are heavily dependent on the nature of secondary amino group in these derivatives. Thus replacement of piperidyl group by bulky dibenzylamino or less nucleophilic diphenylamino group resulted in a drastic decrease in yield of benzaldehyde (entry 4 and 6)

This suggests that reaction of equimolar ethyl benzoate and SDPA rapidly forms two unstable intermediates [1] and [2] by the attack of hydride or piperidyl group on *sp*² carbon of ester, and these are quickly transformed into a more stable intermediate, α -piperidyl alkoxoaluminum [3], by the rearrangement involving migration of piperidyl group or hydride as shown in Scheme 1.

The mechanism is supported by the following facts. (1) Under the same experimental conditions, benzaldehyde was

* This paper is dedicated to Professor Herbert C. Brown on the occasion of his 80th birthday.