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Notes

Exceptionally Facile Reduction of Acid Chlorides to Aldehydes by Sodium Tri-*tert*-butoxyaluminohydride

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The conversion of acid chlorides to aldehydes is one of the most useful synthetic transformations in organic synthesis. Many useful reducing methods have been reported for such conversions,[1] *e.g.*, a catalytic hydrogenation,[2] lithium tri-*tert*-butoxyaluminohydride (LTBA),[3] sodium borohydride in the presence of pyridine,[4] transition metal borohydrides,[5] anionic transition metal reductants,[6] trialkyltin hydrides catalyzed by palladium complexes,[7] organosilicon hydrides,[8] etc.[9] Especially LTBA has been used widely for such purposes because of its simplicity and mildness. However, the reagent cannot achieve a very general reduction of both aliphatic and aromatic acid chlorides.

In the course of examining the reducing characteristics of sodium aluminum hydride (SAH) derivatives, we have found that sodium tri-*tert*-butoxyaluminohydride (STBA) effects the desired transformation in high yields.

Like lithium aluminum hydride (LAH),[3,10] SAH reacts with only 3 equiv of *tert*-butyl alcohol with the evolution of 3 equiv of hydrogen at 0 °C or room temperature, even in the presence of excess alcohol, to form stable sodium tri-*tert*-butoxyaluminohydride (STBA)[11] (eq 1). However,

$$NaAlH_4 + 3t\text{-}BuOH \rightarrow Na(t\text{-}BuO)_3AlH + 3H_2\uparrow \qquad (1)$$

unlike LTBA,[3] STBA is sparingly soluble, even in THF (less than 0.12 M at 0 °C).[12] Among the commercial solvents examined, 2-methoxyethyl ether (diglyme) appeared to be the most useful solvent;[13] it is dissolved up to 0.52 M at 0 °C.

We have discovered that the reagent in diglyme reduces acid chlorides dissolved in THF at −78 °C to the corresponding aldehydes in high yields, which are far superior to those by LTBA. We applied this excellent reducing system to the partial reduction of 22 representative acid chlorides. The results and results by LTBA for comparison are summarized in Table I.

The reagent reduces aromatic acid chlorides **1** examined to aldehydes within 3 h at −78 °C in yields of 85–100%. Various types of substituents, which are susceptible to reduction, can be tolerated, and the yields appear not to be significantly influenced by substituents on the aromatic ring. The reaction of phthalic acid chlorides **2** with 2 equiv of the reagent gave the corresponding dialdehydes in 95–98% yields (Scheme I).

The reduction of aliphatic acid chlorides **3** by this reagent works equally well, giving yields of 92–100%, regardless of structural type. Alicyclic acid chlorides, such as cyclopropane- (**4**) and cyclohexanecarbonyl (**5**) chlorides, are readily converted to the corresponding aldehydes in quantitative yields. The reaction of α,β-unsaturated acid chlorides, such as cinnamoyl chloride (**6**), also undergo the reduction to the corresponding olefinic aldehydes quantitatively. Even aliphatic diacid chlorides, such as adipoyl chloride (**7**), are converted to the dialdehydes in good yields (Scheme I).

It appeared desirable to develop several appropriate procedures for the isolation of aldehydes on the basis of their physical properties: sodium bisulfite adduct meth-

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[12] STBA is almost insoluble in common solvents, such as dimethoxymethane, 1,3-dioxolane, acetonitrile, and ethylene glycol dimethyl ether (DME).

[13] Similarly, STBA is dissolved in triglyme, tetraglyme, or DMF to be around 0.5 M at 0 °C. Methyl sulfoxide dissolves it readily (1.55 M at 25 °C), but the solvent cannot be used in this reduction because of its high freezing point.

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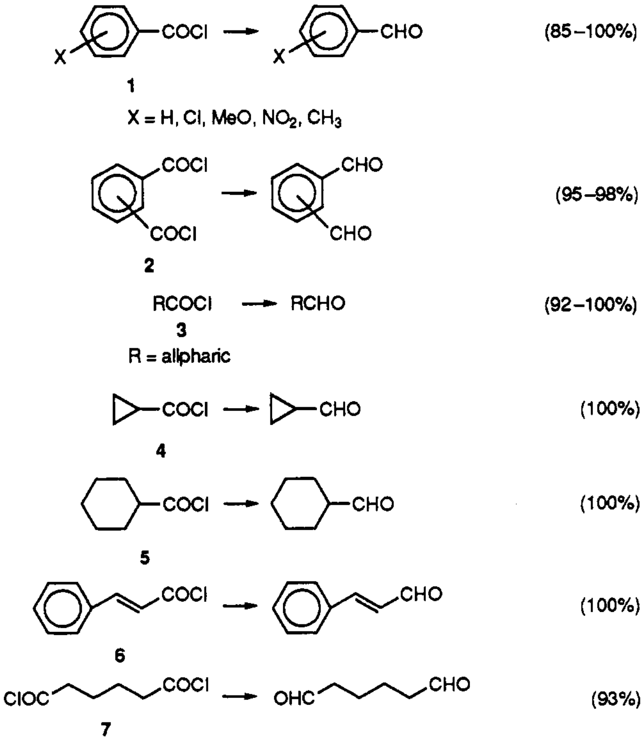
Table I. Yields of Aldehydes in the Reduction of Representative Acid Chlorides with Sodium Tri-*tert*-butoxyaluminohydride in Diglyme–Tetrahydrofuran at -78 °C

acid chloride	yields of aldehydes,[b] %	
	by analysis with (2,4-dinitrophenyl)-hydrazine	by isolation with appropriate method
benzoyl	99 (81)	81[d]
1-naphthoyl	97 (84)	
2-naphthoyl	88 (58)	81[e]
2-chlorobenzoyl	92 (41)	
4-chlorobenzoyl	100 (81)	93[e]
p-toluoyl	100 (61)	87[f]
o-anisoyl	93 (27)	88[c]
m-anisoyl	86 (66)	
p-anisoyl	85 (60)	
4-nitrobenzoyl	100 (84)	89[g]
isophthaloyl	95 (77)	88[e]
terephthaloyl	98 (82)	
butyryl	92 (37)	71[d]
hexanoyl	95 (41)	81[f]
isobutyryl	100 (57)	
trimethylacetyl	96[c] (58)	77[d]
tert-butylacetyl	92[c]	
trichloroacetyl	91	
cyclopropanecarbonyl	100	
cyclohexanecarbonyl	100 (56)	89[d]
cinnamoyl	100 (71)	84[f]
adipoyl	93[c] (53)	

[a] Reacted with an equivalent amount of reagent (1.0 equiv for mono- and 2.0 equiv for dichloride) for 3 h with aromatic and for 1 h with aliphatic acid chlorides, both at -78 °C. [b] Yields are based on the analytically pure products. The figures in parentheses are yields by lithium tri-*tert*-butoxyaluminohydride.[3] [c] Reacted for 3 h at -78 °C. [d] Isolated by the sodium bisulfite adduct method.[14] [e] Isolated by crystallization after evaporation of solvents. [f] Isolated by distillation. [g] Isolated by crystallization on hydrolysis.

Scheme I



od,[14] distillation, and crystallization. Each procedure affords a very good yield of aldehydes.

Experimental Section

General Procedures. The reaction flask and other glassware required for the experiments were predried at 140 °C for several hours, assembled hot, and cooled under a stream of nitrogen. Syringes were assembled and fitted with needles while hot, and then they were cooled. All reactions were carried out under a static pressure of nitrogen in flask fitted with septum-covered side arms with use of standard techniques for handling air-sensitive materials. Tetrahydrofuran (THF) was distilled from sodium–benzophenone ketyl and stored under dry nitrogen. 2-Methoxyethyl ether (diglyme) was distilled from lithium aluminum hydride under nitrogen. Acid chlorides used were commercial products of the highest purity, which were carefully purified by standard methods before use. Sodium aluminum hydride (SAH) was used directly as received from Ethyl Corp. ^{27}Al NMR chemical shifts are with reference to $Al(H_2O)_6^{3+}$.

Preparation of Sodium Aluminum Hydride (SAH) in Diglyme. An oven-dried, 2-L, round-bottom flask with a side arm, equipped with a magnetic stirring bar and an adaptor, was attached to a mercury bubbler. The flask was flushed with dry nitrogen and then maintained under a static pressure of nitrogen. To this flask were added 27 g of SAH (500 mmol) and 600 mL of diglyme. The slurry was stirred for 48 h at room temperature and then allowed to stand to permit the undissolved materials to settle. The supernatent solution was filtered through a fritted-glass funnel and kept under dry nitrogen in cold room. The concentration of SAH was estimated gasometrically to be 0.8 M. The ^{27}Al NMR spectrum of the solution showed a clean quintet centered at δ 97 ppm (J_{Al-H} = 175Hz).

Preparation of Sodium Tri-*tert*-butoxyaluminohydride (STBA) in Diglyme. To an oven-dried, 500-mL flask fitted with a side arm and a reflux condenser leading to a mercury bubbler was added 200 mL of an 0.8 M solution of SAH (160 mmol) in diglyme, and the solution was cooled to 0 °C with an ice–water bath. To this solution was added 36 g of *tert*-butyl alcohol (485 mmol) dropwise with vigorous stirring. After the complete addition, the mixture was stirred for 6 h at 0 °C. The concentration of STBA was estimated gasometrically to be 0.48 M. The ^{27}Al NMR spectrum of the solution showed a broad singlet centered at δ 150 ppm.

Reaction of Acid Chlorides. The following reductions are typical of the procedure utilized in the quantitative analysis with (2,4-dinitrophenyl)hydrazine.

An oven-dried, 100-mL flask fitted with a side arm and a bent adaptor connected to a mercury bubbler was charged with 54 mL of a 1.0 M benzoyl chloride solution (7.86 g, 54 mmol) in THF. The flask was immersed in a cooling bath of dry ice and acetone. A 0.48 M solution of STBA in diglyme (113 mL, 54 mmol) kept at 0 °C was added dropwise using a double-ended needle with vigorous stirring. After the complete addition of the reagent, the reaction mixture was stirred for an additional 3 h at that temperature. An aliquot (4 mmol) of the reaction mixture was withdrawn and subjected to analysis with (2,4-dinitrophenyl-)hydrazine, showing a yield of 99%. The rest of the reaction mixture (50 mmol) was further treated for isolating the aldehyde.

Isophthaloyl dichloride (10.96 g, 54 mmol) in 44 mL of THF was reacted with 108 mmol of the reagent for 3 h at -78 °C in the same manner described above. By estimation as the (2,4-dinitrophenyl)hydrazone, the yield was 95%.

A number of acid chlorides were reduced in the same manner described above, and the yields of the aldehydes were established by the quantitative estimation of the corresponding (2,4-dinitrophenyl)hydrazone. The identity of the hydrazones was checked through their melting points. The yields of the hydrazones are listed in Table I.

Isolation of Aldehydes by the Sodium Bisulfite Adduct Method.[14] The procedure for the adduct formation of benzaldehyde in the reaction mixture and regeneration of the aldehyde is representative. After reaction of benzoyl chloride (54 mmol) with the reagent for 3 h at -78 °C (vide ante), an aliquot of the reaction mixture was withdrawn for analysis with (2,4-dinitrophenyl)hydrazine. Then the remaining reaction mixture was hydrolyzed at room temperature with a sufficient amount of 10% HCl solution (*ca.* 15 mL) to make a clear solution. The mixture was then saturated with solid sodium chloride, and the organic

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layer was separated. The aqueous layer was washed twice with diethyl ether (2 × 30 mL). After being neutralized with a small quantity of solid sodium bicarbonate, the combined organic extracts were poured into 75 mL of a saturated aqueous sodium bisulfite solution. The mixture was stirred for 1 h. At this time the crystalline bisulfite adduct of benzaldehyde was apparent. The solution was cooled in an ice-water bath to ensure complete crystallization of the adduct. The adduct was then collected by filtration, washed with 3 × 25 mL of pentane, and dried. The solid adduct was placed in 50 mL of a saturated aqueous magnesium sulfate solution, and then 50 mL of pentane and 8 mL of a 37% formaldehyde solution were added. The mixture was stirred vigorously for 1 h. The solid adduct slowly disappeared. The pentane layer was then separated and dried with anhydrous magnesium sulfate. Evaporation of all volatile materials gave a 81% yield of benzaldehyde (4.30 g): $n^{24}{}_D$ 1.5450. The ^{1}H NMR spectrum agreed with that of an authentic sample. In the isolation of trimethylacetaldehyde, a slightly modified procedure was adopted. The procedure was actually the same as in the procedure described above, except for the reaction temperature. Thus, the mixture was heated to 90–95 °C for 1 h with stirring. The solid disappeared. The mixture was cooled to room temperature and saturated with magnesium sulfate heptahydrate. The organic layer was separated and dried, and on distillation of the solvent, almost pure trimethylacetaldehyde (3.32 g, 77%) was obtained: $n^{24}{}_D$ 1.3795. The ^{1}H NMR spectrum agreed with that of an authentic sample.

Isolation of Aldehydes by Distillation. Isolation of hexanal is illustrative. In the usual setup, 50 mmol of hexanoyl chloride dissolved in 43 mL of THF was reduced with 50 mmol of the reagent at −78 °C for 1 h, the same as the procedure described previously. After reaction, the mixture was hydrolyzed at room temperature with 20 mL of 10% HCl solution and saturated with solid sodium chloride. The separated aqueous layer was washed twice with diethyl ether (2 × 30 mL). The combined organic extracts were dried with anhydrous magnesium sulfate. The mixture was then subjected to distillation to yield 4.06 g of hexanal (81%): bp 130–131 °C, $n^{24}{}_D$ 1.4032. The ^{1}H NMR spectrum was identical with an authentic sample.

Isolation of Aldehydes by Crystallization. Isolation of 4-nitrobenzaldehyde is representative. In the assembly previously described, 4-nitrobenzoyl chloride (9.28 g, 50 mmol) and 45 mL of THF were placed and reacted with 50 mmol of the reagent (0.48 M, 104 ml) at −78 °C for 3 h. After the reaction was complete, the mixture was poured onto crushed ice. The precipitated solid was filtered, pressed dry, and then extracted three times with 95% ethanol. Distillation of the solvent gave 7.4 g of crude 4-nitrobenzaldehyde (98%): mp 103–5 °C . Recrystallization from hot water gave 6.72 g of light yellow solid (89%): mp 105–6 °C. The ^{1}H NMR spectrum was identical with an authentic sample.

Similarly, isophthaloyl dichloride (10.15 g, 50 mmol) was treated with 100 mmol of the reagent and reacted for 3 h at −78 °C. After hydrolysis with 10% HCl solution, the mixture was saturated with solid sodium chloride and the organic layer was separated. The aqueous layer was washed twice with diethyl ether (2 × 30 mL). The combined organic extracts were dried with anhydrous magnesium sulfate. On evaporation of solvents there was obtained 6.44 g of crude isophthaldehyde (96%). Recrystallization from 95% ethanol produced 5.90 g, a 88% yield, of pure isophthalaldehyde: mp 89–90 °C. The ^{1}H NMR spectrum was identical with an authentic sample.

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