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PREPARATION OF 1-DEUTERIOALDEHYDES VIA THE USE OF DIISOBUTYLALUMINUM DEUTERIDE (DIBAL-D)

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Abstract-- Deuterioaldehydes, essential precursors in the preparation of chiral primary deuterioalcohols, have been prepared in yields ranging from 55-75% via reduction of methyl and ethyl esters at -78°C with diisobutylaluminum deuteride (DIBAL-D). The stoichiometry of the DIBAL-D reduction and the time of the reduction were varied depending upon the structure of the reactant. Aliphatic esters were reduced in 6-10 min. at -78°C while aromatic esters were reacted for 1 hr. at -78°C. From 1.0 to 1.5 equivalents of DIBAL-D were used to reduce simple monofunctional esters while multifunctional esters required 2.0 to 2.5 equivalents of DIBAL-D.

Deuterio- and tritioaldehydes are essential synthetic precursors in the preparation of chiral primary deuterio and tritioalcohols. This is especially true since the development by Midland _et al_ [1] of the chiral reducing agents (+) and (-) _B_-isopinocampheyl-9-borabicyclo[3.3.1]nonanes (commercially available from Aldrich Chemical Company as _R_ and _S_-Alpine boranes® respectively) which have been used to prepare chiral-deuterated primary alcohols in enantiomeric excesses ranging from 70 to 100% from the appropriately deuterated aldehydes.

A variety of synthetic methods for the preparation of 1-deuterioaldehydes have been reported. These procedures are multistep in nature and several require the non-deuterated aldehyde. Examples of these methods include quenching of the lithiated dithiane adduct of an aldehyde with deuterium oxide;[2] reaction of a lithio derivative with an isonitrile, followed by quenching of the lithiated aldimine adduct with deuterium oxide and subsequent hydrolysis;[3] condensation of an aldehyde with 1,2-benzenedithiol, conversion of this adduct into 2-substituted 1,3-benzodithiolium salts, reduction of these salts with either $LiAlD_4$ or $NaBD_4$, and hydrolysis;[4] and finally reaction of Grignard reagents with 2-deuterio-1,3-benzodithiolium perchlorate and subsequent hydrolysis.[5] The above mentioned procedures require the use of lithio[2,3] and Grignard reagents,[5] which can react with a variety of functional groups, as well as the use of such expensive deuterated reagents as dideuteriodichloromethane.[5] Additional synthetic procedures have been developed for the preparation of 1-deuterioaldehydes which do not require as many steps; however, these methods appear to be specific only for preparation of aromatic 1-deuterioaldehydes[6(a-c)]. One can also prepare 1-deuterioaldehydes via the oxidation of the corresponding dideuterioalcohols which are prepared by the reduction of carboxylic acids and carboxylic acid esters with BD_3-THF or $LiAlD_4$ and $LiBD_4$, respectively.[7(a-c)] The dideuterioalcohols can then be oxidized to 1-deuterioaldehydes via the use of such reagents as Ag_2CO_3/celite,[7a,8] pyridinium dichromate,[9] or pyridine-SO_3 complex.[7c] These reagents can be expensive (as in the case of Ag_2CO_3) and all lead to the loss of a deuterium atom in the transformation of the dideuterioalcohol to the 1-deuterioaldehyde. This reduction-oxidation sequence not only requires two steps but two deuterium atoms are utilized in a synthetic sequence where only one is required.

Aldehydes have been prepared directly by the reaction of methyl, ethyl and isopropyl esters with diisobutylaluminum hydride in yields ranging from 40-90% with the yields of aromatic aldehydes usually lower than for aliphatic aldehydes.[10(a-g)] Diisobutylaluminum hydride can reduce esters to aldehydes in the presence of a variety of protected functional groups. For example, esters can be reduced to aldehydes in the presence of ether-protected alcohols, carbamoylated-protected amines (cBz, t-BOC) and tritylated amines[11]. Methyl and ethyl esters can be reduced in the presence of t-butyl esters. This selectivity has been utilized in a synthesis of camptothecine[12].

In this paper, we wish to report on a novel synthesis of 1-deuterioaldehydes from methyl and ethyl esters via the use of DIBAL-D.

RESULTS AND DISCUSSIONS

Deuterioaldehydes (1a-7a) were prepared in isolated analytical yields ranging from 55-75% (See table 1). Aliphatic esters were found to be reduced to aldehydes in 6 to 10 min. at -78°C, while aromatic esters required reaction times of 1 h at these temperatures.

Deuterioaldehyde 1a was prepared in 75% yield directly from ester 1, whereas reduction to the dideuterioalcohol followed by oxidation of the alcohol to the deuterioaldehyde proceeded in an overall yield of 30%. These yields compare with the overall yields reported for the synthesis of N-protected phenylalanal of 48%[13] and 77%[14].

Several precautions should be taken in performing the reduction. The reaction should be both conducted and quenched at low temperatures (-78°C). It is important to control both the reaction time and the stoichiometry of the reducing agent. For simple monofunctional esters, a slight excess (1.1-1.5 equiv.) of DIBAL-D is sufficient for reduction. In the case of multifunctional esters such as (1), it was necessary to use an additional equivalent of DIBAL-D (2.2 equiv.) because of the acidic nature of the hydrogen attached to the carbamate nitrogen. Over-reduction of the ester to the dideuterioalcohol with DIBAL-D can be observed if the above precautions are not observed. If large amounts of dideuterioalcohols are obtained, the alcohol can be readily separated from the aldehyde by column chromatography. The dideuterioalcohol may then be oxidized to the 1-deuterioaldehyde by any of the previously mentioned procedures.[7c, 8]

As seen by the results presented here, DIBAL-D is a powerful reagent for the direct preparation of 1-deuterioaldehydes from methyl and ethyl esters. A dideuterioalcohol does not have to be prepared, nor is it necessary to rely on a multistep sequence in which the non-deuterated aldehyde is required as starting material. This methodology is extremely useful in the preparation of precursors to chiral primary deuterioalcohols as well as in the synthesis of N-protected α and β amino deuterioaldehydes from α and β amino acids. In addition, with the availability of LiT, this procedure can be utilized for the preparation of chiral primary tritioalcohols via the preparation of 1-tritioaldehydes. These necessary aldehydes can be obtained by reaction of the appropriate ester with diisobutylaluminum trituride (DIBAL-T).[15]

EXPERIMENTAL

Melting points were determined on a Mel-Temp apparatus and are uncorrected. Semicarbazone derivates were prepared by the method of Shriner et al.[16] Compounds 2 to 6 were purchased from Aldrich Chemical Co. and were used without further purification. Compound 1 was prepared from 3-amino-3-[4'-methoxyphenyl]-1-propanoic acid.[17] Compound 7 was prepared from phenoxyacetic acid. Diisobutylaluminum chloride and LiD (98%+) were purchased from THIOKOL/Ventron Division.

TABLE 1: Physical Data and Yields of 1-Deuterioaldehydes Prepared by DIBAL-D Reduction

Ester	Aldehyde[a]	Yield % [b]	mp °C [c] Semicarbazone (lit.)[d]
$CH_3O(C_6H_4)CH(NHBOC)CH_2COOCH_3$ 1	$CH_3O(C_6H_4)CH(NHBOC)CH_2CDO$ 1a	75	_[e]
$CH_3(CH_2)_{10}COOC_2H_5$ 2	$CH_3(CH_2)_{10}CDO$ 2a	75	98-100 (103,106)
$CH_3(CH_2)_6COOC_2H_5$ 3	$CH_3(CH_2)_6CDO$ 3a	70	96-97.5 (95,104)
$CH_3(CH_2)_7COOC_2H_5$ 4	$CH_3(CH_2)_7CDO$ 4a	70	95-97 (100,84)
$C_6H_5COOCH_3$ 5	C_6H_5CDO 5a	65	215-217 (222,233)
$C_6H_5CH_2COOCH_3$ 6	$C_6H_5CH_2CDO$ 6a	55	142-145 (153-156)
$C_6H_5OCH_2COOCH_3$ 7	$C_6H_5OCH_2CDO$ 7a	72	_[f]

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a) % Deuterium incorporation for compound 1a was 99.9% as determined by mass spectral analysis and for compounds 2a - 7a were 100% based upon ^1H-nmr integration of the aldehydic hydrogen.

b) isolated, analytical yield.

c) mp uncorrected.

d) Literature mp as reported in CRC Handbook of Organic Compound Identification. 3rd ed. (1967) Chemical Rubber Co.

e) No semicarbazone was prepared; C, H, analysis (see experimental section) indicated that compound 1a was the aldehyde.

f) Semicarbazone was not prepared; Bp. 80-81°C (1.4 torr) compares with lit. value 94°C (6 torr) Hatch, L.F., Nesbit, S.S., J. Am. Chem. Soc. (1945) 67 39-41.

Percent deuterium incorporation of 1-deuterioaldehydes 2a through 7a were determined from NMR spectral data. NMR spectra were obtained on a Varian EM-360 60 MHz NMR spectrometer. Percent deuterium incorporation of 1a was determined from mass spectral data obtained on a Finnigan 4021 mass spectrometer (Chemistry Department, University of Michigan). Toluene and hexane were distilled from sodium metal. Methanol was dried over magnesium turnings and distilled from a magnesium methoxide slurry. Anhydrous diethyl ether (Mallinckrodt) was used without further purification. Rochelle salt (sodium potassium tartrate - tetrahydrate) was dissolved in deionized water and used as a saturated solution (66 g/100mL).

Preparation of diisobutylaluminum deuteride (DIBAL-D).

DIBAL-D was prepared by the procedure of Eisch *et al.*[18] with the following modifications. A 3-necked 500 mL round bottom flask (flame-dried under nitrogen) was fitted with a sealed, overhead *mechanical* stirrer; a nitrogen inlet; a 250 mL constant pressure addition funnel and a Friedrichs condenser. The 500 mL round bottom flask was then charged with 3.20 g (0.356 moles) of powdered LiD and 80 mL of anhydrous ether. The suspension was vigorously stirred, cooled to 0°C, and to the slurry was added dropwise 200 mL (0.250 moles; 44.0 g) of a 25% (wt/wt) diisobutylaluminum chloride solution in hexane. After addition of the diisobutylaluminum chloride solution, the reaction mixture was warmed to room temperature, and then heated to reflux (with constant stirring) for 48 h under nitrogen. The reaction mixture was then cooled to room temperature and the stirring discontinued. The insoluble LiCl was allowed to settle to the bottom of the reaction vessel and an aliquot of the hexane/ether solution was removed. The solvent of the aliquot was evaporated; the residue was dissolved in aqueous nitric acid; and to the resulting solution was added a silver nitrate solution. A slight precipitate (AgCl) was observed. An additional 0.250 g (.0278 moles) of LiD was then added to the reaction and the mixture was then stirred at reflux temperature under nitrogen for an additional 48 h. The slurry was then cooled to room temperature and the liquid rechecked for residual chloride as described above. The solution was then transferred under a nitrogen atmosphere via transfer needle to an oven-dried, brown bottle which was fitted with a rubber septum. The hexane/ether solution of DIBAL-D was stored at room temperature under nitrogen. Note: DIBAL-D is extremely sensitive to air and moisture.

Standardization of DIBAL-D. The molarity of the DIBAL-D solution was determined by a modification of the procedure of Aldrich Chemical Co.[19] A 250 mL 3-necked round bottom flask was fitted with two rubber septa, a magnetic stir bar, and a reflux condenser. The reflux condenser was attached by tygon tubing to a three-way stopcock connected to the top of an inverted graduated buret filled with water. The bottom of the inverted buret was attached with tygon tubing to a leveling bulb which was also filled with water. With the three-way stopcock opened to the atmosphere, the leveling bulb was positioned so that the water contained in the leveling bulb was at the same level as the water in the inverted buret. The three-way stopcock was then closed to the atmosphere and a portion of the DIBAL-D solution (0.600- 0.800 mL) was injected into the 250 mL round bottom flask which was charged with a 4:1:1 (v:v:v) biphasic solution of hexane:H_2O:HCl (conc). After the generated hydrogen gas (HD) had displaced the water in the inverted buret, the leveling bulb was moved up and down several times until the height of the water remaining in the buret was equal to the level of water in the leveling bulb. The difference between the initial and final water level readings was used to calculate the molarity of the DIBAL-D solution. An average of five separate determinations was used for this calculation.[19]

Preparation of 1-deuterioaldehydes. The 1-deuterioaldehydes were synthesized by the following procedures:

A 250 mL round bottom flask (flame-dried under nitrogen) which was fitted with a magnetic stir bar, a rubber septum and a nitrogen inlet was charged with 50 mL of dry toluene and 2.00 g (6.82×10^{-3} moles) of 3-amino t-butyloxycarbonyl-3-(4'-methoxyphenyl) 1-propanoic acid methyl ester (1). The stirred solution was then cooled to -78°C and 7.10 mL (0.0143 moles) of a 2.02 M DIBAL-D solution in hexane/ether was then added dropwise. The solution was then stirred for 6 min. at -78°C and then quenched at -78°C with 8 mL of dry methanol and 15 mL of saturated aqueous Rochelle salt. The mixture was then allowed to warm to room temperature and diluted with 150 mL of ether. The aqueous layer was extracted (3 x 150 mL) with ether. The combined ether extracts were dried ($MgSO_4$); the solvents were removed *in vacuo*; and the oil was placed under high vacuum at room temperature to remove residual toluene. The oil was then dissolved in ethyl acetate and evaporated onto 3.5 g of silica gel (Merck 70-230 Mesh). The silica gel containing the pre-absorbed product was then placed on a chromatography column containing 40 g of silica gel and eluted with hexane/ ethyl acetate (4:1) . The fractions containing 1-deuterioaldehyde 1a were combined and the solvent removed *in vacuo* to afford 1.35g (75%) of a white crystalline solid. mp 90-91°C.

NMR $CDCl_3$/TMS: δ 1.50 (s, 9H, *t*-Butyl), 2.95 (m, 2H,-$C\underline{H}_2$-), 3.80 (s, 3H, -$OC\underline{H}_3$), 5.20 (m, 2H, -$C\underline{H}$-; -$N\underline{H}$-), 6.80-7.40 (m, 4H, Ar$\underline{H}$)[20]

Anal. Calcd. for $C_{15}H_{20}DNO_4$ C, 64.27, H, 7.19; Found: C, 64.47 H, 7.55.

Deuterioaldehydes 2a to 7a were prepared in a manner similar to that described for 1a. Esters 2 to 7 were reacted with 1.0-1.5 equivalents of DIBAL-D at -78°C. Esters 2,3,4 and 6 were reacted with DIBAL-D for 10 min, while esters 5 and 7 were reacted with DIBAL-D for 1 hr. The reaction mixtures were quenched at -78°C with anhydrous methanol, filtered through celite, and extracted with dilute HCl. The product deuterioaldehydes were purified by column chromatography or vacuum distillation and isolated in yields ranging from 55-75% (see table).

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14. Homada *et al*. (ref. 6c) reported an overall yield of 77% in the synthesis of CBz-L-Phe-al from CBz-L-Phe via reduction-oxidation.

15. Diisobutylaluminum trituride (DIBAL-T) can be prepared from the reaction of diisobutylaluminum chloride with lithium trituride in a method analogous to the one reported in this paper.

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20. Compound **1** was reduced with DIBAL-H to afford the non-deuterated aldehyde which had an NMR spectrum identical to 1-deuterioaldehyde **1a** except that it contained an additional peak at δ 9.70 (s, 1H, -C**H**O).