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Preparation of 1-Deuteriobenzaldehydes by Lithium Aluminum Deuteride Reduction of N-*t*-Butylbenzamides

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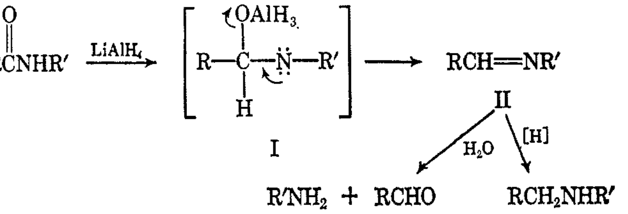
The normal product resulting from the treatment of an amide with lithium aluminum hydride is the corresponding amine.[2] However, numerous investigators have reported the concomitant formation of significant amounts of aldehyde[3] and alcohols[4] under the reaction conditions. Often the formation of aldehydes becomes the major course of the reaction.[5–7] This is readily understandable if one views the reaction as proceeding by the addition of the hydride reagent to the amide carbonyl group to give a derivative of a geminal amino alcohol (I). Elimination from this intermediate yields an aldimine (II) which on hydrolysis affords the aldehyde or, on further reduction, produces the amine.



The need for 1-deuteriobenzaldehydes in connection with other work led us to investigate procedures for the preparation of labeled aldehydes from amides. The recognized[8] sensitivity of hydride reductions to steric factors suggested the possibility that the reduction could be arrested at the aldimine stage if the effective hydride source (I) and the intermediate (II) contained sufficiently bulky substituents close to the reaction site. The lithium aluminum deuteride reduction of N-*t*-butylbenzamides proved to be a convenient route to the desired 1-deuteriobenzaldehydes. The necessary amides were readily prepared by the reaction of the corresponding acid chlorides with *t*-butylamine.

Optimum yields of aldehyde were obtained when equimolar amounts of lithium aluminum deuteride and amide in ether solution were heated under reflux for 15 hr. The use of a lower ratio of deuteride to amide resulted in the recovery of much unconverted amide, while increased reaction time appears to have a negligible, if any, effect on the yields. Increasing the molar ratio of deuteride to amide to 1.5 causes the complete reduction of the imine to the corresponding N-*t*-butylbenzylamine and no aldehyde is obtained when the reduction product is treated with 5% HCl.

Several methods[9] are available for the preparation of benzaldehyde-1-*d*. The method described in the present work has been successfully applied to the synthesis of the following 1-deuteriobenzaldehydes with the indicated yields: anisaldehyde (57%), *p*-tolualdehyde (58%), and benzaldehyde (33%). The convenience of this method compares favorably with the alternate procedures.

Experimental Section[10]

The following procedure is typical.

N-*t*-butylanisamide.—To a cooled, stirred solution of *t*-butylamine (16.4 g, 0.22 mol) in 60 ml of ether was added a solution of anisoyl chloride (17.1 g, 0.10 mol) in 60 ml of ether over a period of 2 hr. The precipitated amine hydrochloride was removed by filtration and the ethereal solution containing the amide was washed with water and dried over anhydrous sodium sulfate. Removal of the ether gave 19.2 g of crude material which was recrystallized from hexane–chloroform to afford 12.6 g (60%) of N-*t*-butylanisamide, mp 116–117°.

Anal. Calcd for $C_{12}H_{17}NO_2$: C, 69.54; H, 8.27; N, 6.76. Found: C, 69.41; H, 8.18; N, 6.85.

N-Anisylidene-*t*-butylamine.—To a stirred slurry of lithium aluminum deuteride (1.26 g, 0.030 mol) in 100 ml of anhydrous ether was added a solution of N-*t*-butylanisamide (5.18 g, 0.025 mol) in 150 ml of anhydrous ether over a 30-min period. The reaction mixture was heated under reflux for 15 hr after which the reaction was quenched by the cautious addition of 5 ml of water followed by 3 ml of 10% sodium hydroxide. The ether layer was concentrated on a rotary evaporator to give 4.78 g of a colorless oil. The nmr spectrum of the oil indicated its composition to be 90% aldimine (CH_3 singlet, 1.28 ppm), 5% unreacted amide (CH_3 singlet, 1.46 ppm), and 5% amine (CH_3 singlet, 1.16 ppm).

Anisaldehyde-1-*d*.—The crude aldimine (4.78 g) obtained from the lithium aluminum deuteride reduction was stirred at 70° with 60 ml of 5% hydrochloric acid for 30 min. The imine hydrochloride which precipitated initially was gradually converted to an insoluble oil. The reaction mixture was cooled to room temperature and extracted with 75 ml of ether. The ether extract was washed with 5% sodium hydroxide, followed by water, dried over anhydrous sodium sulfate, and concentrated on a rotary evaporator to give 2.43 g (71%) of a colorless oil. The nmr spectrum showed this material to be essentially pure anisaldehyde-1-*d*. Distillation gave a colorless oil (1.96 g, 57%), bp 76° (0.6 mm). The infrared spectrum showed a C–D stretching doublet at 2050 and 2100 cm^{-1} and no aldehyde proton could be detected by nmr analysis.

Registry No.—Lithium aluminum deuteride, 14128-54-2.

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[1] Participant in National Science Foundation Undergraduate Research Program, Summer 1967.

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[10] Melting points are corrected and boiling points are uncorrected. Infrared spectra were determined with a Perkin-Elmer Infracord Model 137 infrared spectophotometer. Nmr spectra were determined with a Varian Associates A-60 spectrometer and absorptions are reported in parts per million (ppm) relative to tetramethylsilane for 15% solutions in deuteriochloroform.