Reduction of Some Grignard Reagent–Carbon Dioxide Adducts to Primary Alcohols by Lithium Aluminum Hydride

By Alex P. Mathers and Maynard J. Pro

Reduction of carboxylic acids to alcohols by lithium aluminum hydride[1,2] has been studied extensively owing to the fact that most of these acids are quite resistant to other reducing agents. No references were found where lithium aluminum hydride was used to reduce a halomagnesium alkanoate directly to an alcohol.

Tuot[3] describes the conditions necessary for obtaining high yields of acids from the reaction of carbon dioxide and Grignard reagents. Since the same conditions were found to apply in the production of alcohol from the halomagnesium alkanoate, precautions were taken to prevent secondary reactions. Approximately 1 N Grignard reagent was prepared and held at -20 to $-30°$ during the admission of carbon dioxide, which was added in excess as rapidly as possible.

Side reactions in the case of the lower molecular weight alkyl groups are suppressed by the insolubility of the halomagnesium alkanoate which precipitates in the ether solution. With the higher molecular weight alkyl groups, the reaction mixture remains homogeneous, but the addition of a second or third alkyl group to the carbon dioxide is apparently slow.

Ketones, secondary and tertiary alcohols are three possible impurities of the Grignard reaction between alkylmagnesium halide and carbon dioxide followed by reduction with hydride. Some of these have boiling points near those of the primary alcohols, thus necessitating various isolation procedures.

Experimental

Syntheses of ethanol, n-propyl alcohol, 3-methylbutanol-1 and 7-methyloctanol-1 from methyl iodide, ethyl bromide, 1-chloro-2-methylpropane and 2-bromo-n-octane, respectively, entailed identical procedures in the preparation of the Grignard reagent, halomagnesium alkanoate, lithium aluminum hydride reagent, reduction of the Grignard complex and the hydrolysis of the reduced compounds to the alcohols.

Magnesium turnings (0.55 mole) were placed in a three-necked one-liter flask and covered with 100 ml. of anhydrous ether. The alkyl halide (0.5 mole) in 300 ml. of ether was added slowly with stirring and the mixture was refluxed for one hour after the final addition of alkyl halide.

The reaction flask was placed in a Dry Ice–acetone-bath at -20 to $-30°$ and the dropping funnel used for addition of the alkyl halide was exchanged for an inlet tube extending beneath the surface of the ether. A flask containing approximately 75 g. of Dry Ice was attached to the inlet tube and by slight warming about half the carbon dioxide was admitted rapidly to the reaction vessel. The remaining carbon dioxide was admitted slowly while the flask and contents were allowed to come to room temperature. Vigorous stirring was maintained throughout the addition of carbon dioxide.

A slurry of lithium aluminum hydride 0.5 mole was prepared in 200 ml. of absolute ether. The lithium aluminum hydride was carefully powdered under an atmosphere of nitrogen, ether added and the mixture refluxed for three hours. This unfiltered slurry was slowly added to the halomagnesium

alkanoate with continuous stirring, at such a rate that ether reflux was maintained. Refluxing was continued for three hours after addition of the slurry.

The reaction mixture was cooled to $0°$ in an ice-bath and water very cautiously added to destroy the excess hydride. Stirring was vigorous during the addition of water to prevent the possibility of a sudden excess of water causing the reaction to become violent. Following this addition, solid material in the flask was dissolved in 15 to 20% sulfuric acid. The alcohols were recovered by extraction and fractional distillation.

Both aqueous and ethereal portions of the ethanolic solution were fractionated through a packed column with high reflux ratio. When the ether was almost completely removed the still was placed under total reflux and a slow stream of air was admitted through the still head to sweep out the last traces of low boiling components. The air line was disconnected and the distillate between 78 and 79° was collected.

For recovering the n-propyl alcohol, the ether layer was separated and the aqueous portion fractionated. The distillate below 95° was added to the ethereal solution. This solution was washed with 10 ml. of water, then dried for two hours with anhydrous potassium carbonate. Most of the ether was removed at atmospheric pressure through a packed column by a procedure similar to that used for the ethanol. The distillate recovered between 90 and 100° was fractionated at 50 mm. and again at 20 mm. pressure. The receiver was immersed in an ice–salt-bath.

The 3-methylbutanol-1 was separated from the aqueous portion by ether extraction, the ether solution washed with 10 ml. of water and dried with anhydrous potassium carbonate. The ether was removed as above and the alcohol fractionated at 15 mm. pressure.

The 7-methyloctanol-1 was recovered by the same procedure as the 3-methylbutanol-1 except fractionation was at 10 mm.

Alcohol	Yield, %	Refractive index $n^{25}D$	3,5-Dinitrobenzoate M.p., °C.	B.p, (760 mm.)
Ethanol	74	1.36181	91.5–93	78.0
n-Propyl alcohol	78	1.38375	74	97.0
3-Methylbutanol-1	75	1.40460	60–61	130–132
7-Methyloctanol-1	73	1.43160	47–48	209–210

Internal Revenue Service
U. S. Treasury Dept.
Washington 25, D. C.

Components of Podophyllin. XV. Pyrolysis of Podophyllotoxin Halides[1]

By Anthony W. Schrecker, Gertrude Y. Greenberg and Jonathan L. Hartwell

Thermal decomposition of picropodophyllin (PP) benzoate (I, R = $OCOC_6H_5$) yields α-apoPP,[2] which on further heating undergoes double bond shift to β-apoPP (II, R = CH_3).[2-4] Analogously, podophyllotoxin (PT) benzoate should yield β-apoPP via α-apoPT, the unknown C_3-epimer[1] of α-apoPP. However, either because of the instability of the postulated intermediate[1] or because of a higher temperature needed in this case for the decomposition,[2] only the stable end-product was obtained.[3] Therefore, pyrolytic dehydrohalogenation of the PT halides (I, R = Cl or Br)[5] was carried out since their decomposition temperatures[5] are much lower than those of the carboxylic

(1) A. E. Finholt, G. J. Nystrom, H. C. Brown and H. I. Schlesinger, "Symposium on Hydrides," Amer. Chem. Society, Sept. 10, 1946.

(2) W. G. Brown, "Organic Reactions," Vol. VI, John Wiley and Sons, Inc,. New York, N. Y., 1951, pp. 469–509.

(3) M. Tuot, Compt. rend., 208, 1026 (1939).

(1) Paper XIV: A. W. Schrecker and J. L. Hartwell, This Journal, 76, 752 (1954).

(2) A. W. Schrecker and J. L. Hartwell, ibid., 75, 5916 (1953).

(3) N. L. Drake and E. H. Price, ibid., 73, 201 (1951).

(4) A. W. Schrecker and J. L. Hartwell, ibid., 74, 5676 (1952).

(5) J. L. Hartwell and A. W. Schrecker, ibid., 73, 2909 (1951).