Reduction of Carboxylic Acids with Sodium Borohydride and an Electrophile

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Since its discovery over forty years ago (*1*), sodium borohydride, NaBH$_4$, has been exhaustively studied. Standard organic chemistry texts discuss the lower reactivity of NaBH$_4$ compared with lithium aluminum hydride, LiAlH$_4$: whereas LiAlH$_4$ reduces carboxylic acids to primary alcohols, NaBH$_4$ does not reduce carboxylic acids. This differentiation is the basis of a recent experiment described in this *Journal* (*2*).

Three recent articles (*3–5*) led us to investigate the reaction of sodium borohydride with carboxylic acids. These reports show that after initial addition of the carboxylic acid to NaBH$_4$, subsequent addition of an electrophile, either I$_2$ (*3, 5*) or H$_2$SO$_4$ (*4*), reduces the carboxylic acid to the primary alcohol. The probable mechanism is shown in Figure 1. The intermediate **2** is not susceptible to hydride attack at carbonyl carbon, but **2** does react with the added electrophile "E$^+$", producing intermediate **3**. The left resonance form of **3** shows that trivalent boron serves to withdraw electrons from the adjacent oxygen, leaving the carbonyl carbon susceptible to nucleophilic attack by hydride. This proposed mechanism also explains the observation (*6*) of aldehydes **4** produced in some borohydride reducing media.

Our goal was to develop the new reduction conditions into a procedure applicable to the first-year organic chemistry laboratory, where reduction of the carboxylic acid group has remained an obstacle, notwithstanding the use of borane or LiAlH$_4$ (*2*) on the microscale. The NaBH$_4$ method with either electrophile can be modified to any scale; in our hands, the use of I$_2$ as the electrophile performed better at the semimicro scale than the H$_2$SO$_4$ method.

Using tetrahydrofuran (THF) as solvent gives higher yields than diethyl ether or dimethoxyethane (glyme), and THF does not need to be dried before use, unlike conditions for LiAlH$_4$ reactions. However, a small amount of THF is cleaved in the reaction, producing 4-iodobutan-1-ol; this by-product is removed with an aqueous ammonia extraction. **CAUTION: As with any hydride reaction,** *hydrogen gas is evolved and must be kept away from ignition sources to avoid explosion.* Stoichiometrically, five hydrides are required to reduce one carboxylic acid: the first to neutralize RCOOH, the second to react with added I$_2$, the third to neutralize the HI produced, the fourth to reduce **3** to **4**, and the fifth to reduce **4** to **5**. Thus 1.25 mol of NaBH$_4$ and 0.5 mol of I$_2$ are required per mole of carboxylic acid. As is typical for borohydride reactions, a significant excess of reagents is used to assure complete reduction (*5*).
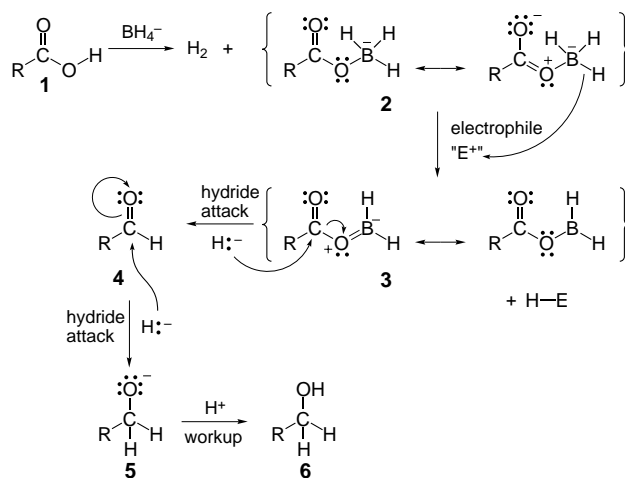
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Figure 1. Probable mechanism of reduction.

Experimental Procedure

Reaction

The apparatus consists of a 100-mL round-bottom flask with magnetic stir bar and Claisen adapter. In the center joint of the Claisen adapter is an open dropping funnel; in the side joint is a cold-water condenser open to the air. To a stirred suspension of fresh, powdered NaBH$_4$ (0.68 g, 18 mmol) in THF (10 mL) in the round-bottom flask is added dropwise over 5 min a solution of diphenylacetic acid (**7**, 2.0 g, 9.4 mmol) in THF (10 mL). **CAUTION: Hydrogen gas is flammable.** The mixture is stirred until gas evolution ceases, about 5 min. A solution of iodine (2.1 g, 8.2 mmol) in THF (15 mL) is added dropwise into the stirred mixture over 15 min, causing evolution of H$_2$ gas, a significant exotherm, and disappearance of the red color of iodine. The solution is heated to reflux with stirring for 45 min or until TLC on silica gel in dichloromethane shows the absence of starting material.

Workup

Approximately 30 mL of THF is distilled from the reaction mixture to avoid emulsions later, leaving a suspension of white precipitate. To the cooled suspension is added cyclohexane (40 mL) and 10% aqueous sodium hydroxide (20 mL). The solution is stirred vigorously until gas evolution ceases and the precipitate is dissolved. It is then transferred to a separatory funnel. The cyclohexane layer is washed 3 times with 20-mL portions of 3M NH$_3$ (aq), once with 20 mL of 12% NaHSO$_3$ (aq)

(to remove any I_2), and once with 20 mL of saturated aqueous sodium chloride, and dried over anhydrous magnesium sulfate. Evaporation of the solvent gives crude 2,2-diphenylethanol (**8**) as a slightly yellow, viscous liquid; typical crude yield is 1.30 g (70% of theoretical). The low-melting product (lit. mp 64–65 °C) usually does not solidify because of residual cyclohexane or traces of the reaction by-product, 4-iodobutan-1-ol. An NMR integration of the crude product can be used to quantitate the amount of each component in the mixture. The ^{1}H NMR of pure **8** shows 10 aromatic hydrogens from δ7.20 to δ7.35, both the CH and CH_2 accidentally equivalent at δ4.2, and the OH variable, usually between δ1.5 and δ2.0; ^{13}C NMR peaks appear at δ141, 129, 128, 127, 66, and 54. The ^{1}H NMR of 4-iodobutan-1-ol shows peaks at δ3.6 (t, 2H), 3.2 (t, 2H), 1.9 (p, 2H), and 1.6 (p, 2H), with the OH variable; ^{13}C NMR peaks appear at δ62, 33, 30, and 7.

If the product does not solidify overnight in an open container, it may be necessary to remove traces of solvent by some combination of: (i) applying high vacuum; (ii) dissolving the product in dichloromethane and reevaporating; and (iii) triturating with chilled 30–60 petroleum ether. Typical pure yield after trituration is 1.00 g (54% of theoretical) with melting point 59–60 °C.

Disposal of Waste

To our knowledge, none of the water-soluble materials is hazardous. All waste products and solvents should be disposed of in an environmentally responsible manner consistent with local regulation.

Acknowledgments
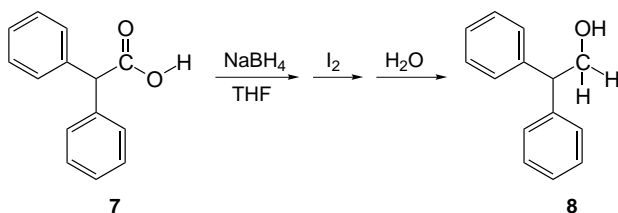
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