Direct Borohydride Reduction of Alcohols to Alkanes with Phosphonium Anhydride Activation

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The phosphonium anhydride reagent, $(Ph_3P^+)_2O$, $2CF_3SO_3^-$, was developed[1-3] as a potent oxophile for reactions involving net loss of water. With this reagent, alcohols react immediately to form the activated phosphonium ether for subsequent elimination[2] or substitution[3] with nucleophiles, as in eq 1. The triflate counterion is

$$ROH + (Ph_3P^+)_2O \rightarrow Ph_3PO + ROP^+Ph_3 \rightarrow RNu \quad (1)$$

not nucleophilic and so allows substitution by added external nucleophiles without unwanted side reactions.

The simplicity of carrying out all the operations quickly in one vessel suggests a practical advantage for the reduction of alcohols, which is normally a multistep procedure.[4] Our initial survey of the borohydride reduction of these phosphonium ethers (eq 1: Nu = H) shows both the value of this reaction as well as some of its limitations. Although the Mitsunobu activation of alcohols with azodicarboxylate and triphenylphosphine is thought to create the same intermediate phosphonium ethers,[5] in our hands no reduction with borohydride was observed under Mitsunobu conditions.

The examples in Table I show that borohydride will reduce primary and acyclic secondary alcohols activated as their phosphonium ethers. The reaction is carried out just with a slurry of sodium borohydride in dichloromethane; no advantage in yield accrued on using soluble quaternary ammonium borohydrides (or added quaternary phase-transfer agents), although the reaction may be faster. The resultant triphenylphosphine oxide is readily removed by passing the reaction mixture through a short plug of silica.

With alcohols which can stabilize the carbocation, the initial phosphonium ether may ionize easily and the borohydride merely serves as a base to afford elimination. This was observed in both 1-phenethyl alcohol and in 1-phenyl-2-propanol (Table I) as well as the instant blackening of cinnamyl alcohol on addition of the reagent even at −78 °C. With the allylic alcohols geraniol and farnesol, however, reduction of both the alcohol group and the allylic double bond occurred.

With cyclic secondary alcohols, however, the reaction appears to be severely limited, apparently by steric hindrance to the S_N2 reaction, since the only product isolated besides the starting alcohol was the complex $Ph_3P{\cdot}BH_3$, which is stable under these conditions. This presumably arises by initial attack of hydride at phosphorus in the phosphonium ether, releasing the starting alcohol and the complex, as in eq 2. There was no reaction

$$ROPPh_3^+ + BH_4^- \rightarrow ROBH_3^- + Ph_3PH^+ \rightarrow ROH + Ph_3P{\cdot}BH_3 \quad (2)$$

of borohydride with the phosphonium anhydride reagent itself under the same conditions, but when menthol was added to the mixture, the complex formed as in eq 2.

Table I. Borohydride Reduction of Alcohols[a]

starting material	product(s)	% yield
benzyl alcohol	toluene	90
1-phenyl-2-ethanol	ethylbenzene	87
1-phenyl-3-propanol	*n*-propylbenzene	90
1-phenyl-3-butanol	*n*-butylbenzene	89
benzhydrol	diphenylmethane	94
N-(β-hydroxyethyl)aniline	*N*-ethylaniline	87
1-phenyl-1-ethanol	styrene	85
1-phenyl-2-propanol	propenylbenzene + allylbenzene (7:3)	85
4-*tert*-butylcyclohexanol, menthol, cholesterol	recovered unchanged	

[a] All reactions in CH_2Cl_2 or $CDCl_3$ with $NaBH_4$ at room temperature for 5 h or less; isolation by chromatography.

Experimental Section

***n*-Propylbenzene.** To a solution of 5.56 g (20 mmol) of triphenylphosphine oxide in 30 mL of dry methylene chloride at 0 °C was added dropwise a solution of 1.57 mL (10 mmol) of triflic anhydride in 30 mL of dry methylene chloride. After 15 min when the precipitate appeared, a solution of 1.36 g (10 mmol) of 3-phenyl-1-propanol in 10 mL of dry methylene chloride was added and the precipitate vanished in 5 min. An amount of 1.5 g (40 mmol) of sodium borohydride was added as a solid all at once and the slurry was stirred at room temperature for 4.5 h. The mixture was washed twice with 1 N HCl and then water and brine, dried over $MgSO_4$, and passed through a short plug of silica to remove triphenylphosphine oxide. Evaporation afforded 1.07 g (89%) of phenylpropane as a colorless liquid: ^1H NMR ($CDCl_3$) δ 7.3–7.1 (m, 5H, Ar*H*), 2.5 (t, 2H, ArCH_2), 1.6 (m, 2H, CH_2CH$_3$) 0.95 (t, 3H, CH_3); ^{13}C NMR δ 143.4, 129.2, 128.9, 126.3 (Ar), 38.8 (ArCH_2), 25.3 (CH_2CH$_3$), 14.6 (CH_3).

Toluene: 90% yield; ^1H NMR ($CDCl_3$) δ 7.2 (m, 5H, Ar*H*), 2.33 (s 3H, CH_3); ^{13}C NMR δ 137.8, 128.9, 128.2, 125.2 (Ar), 21.4 (CH_3).

Ethylbenzene: 87% yield, ^1H NMR ($CDCl_3$) δ 7.3–7.1 (m, 5H, Ar*H*), 2.73 (q, 2H, ArCH_2), 1.22 (t, 3H, CH_3); ^{13}C NMR δ 144.17, 128.26, 127.80, 125.54 (Ar), 28.9 (ArCH_2), 15.6 (CH_3).

***n*-Butylbenzene:** 89% yield; ^1H NMR ($CDCl_3$) δ 7.25 (m, 3H, Ar*H*), 7.15 (m, 2H, ArH), 2.69 (t, 2H, ArCH_2), 1.6 (m, 2H, CH_2CH$_2$CH$_3$), 1.35 (m, 2H, CH$_2$CH_2CH$_3$) 0.95 (t, 3H, CH_3); ^{13}C NMR δ 142.8, 128.3; 128.1, 125.5 (Ar), 35.7 (ArCH_2), 33.6 ((m, 2H, CH_2CH$_2$CH$_3$)), 22.4 (m, 2H, CH$_2$CH_2CH$_3$), 13.9 (CH_3).

Diphenylmethane: 94‰ yield; ^1H NMR ($CDCl_3$) δ 7.25 (m, 10H, Ar*H*), 3.95 (s, 2H, CH_2); ^{13}C NMR δ 141.0, 128.9, 128.4, 125.9 (Ar), 46.9 (CH_2).

***N*-Ethylbenzene:** 87% yield; ^1H NMR ($CDCl_3$) δ 7.15 (t, 2H, Ar*H*), 6.66 (t, 1H, Ar*H*), 6.58 (d, 2H, Ar*H*), 3.49 (s, broad, 1H, D_2O exch, N*H*), 3.10 (q, 2H NHCH_2), 1.20 (t, 3H, CH_3); ^{13}C NMR δ 148.9, 129.1, 117.1, 112.65 (Ar), 38.38 (NHCH_2), 14.83 (CH_3).

Styrene: 85% yield; ^1H NMR ($CDCl_3$) δ 7.35 (m, 2H, Ar*H*), 7.25 (m, 3H, Ar*H*), 6.7 (dd, 1H, vinyl), 5.71 (d, 1H, vinyl), 5.20 (d, 1H, vinyl); ^{13}C NMR δ 137.5, 128.5, 127.7, 126.1 (Ar), 136.9 (ArCH), 113.7 (CH_2).

Propenylbenzene (α-methylstyrene): ^1H NMR ($CDCl_3$) δ 7.45 (m, 2H, Ar*H*), 7.30 (m, 3H, Ar*H*), 5.35 (s, 1H, ArC*H*), 5.08 (s, 1H, C*H*CH$_3$), 2.15 (s, 3H, CH_3); ^{13}C NMR δ 143.2, 128.7, 127.3, 125.4 (Ar), 141.2 (ArCH), 112.3 (CHCH$_3$) 21.8 (CH_3).

Allylbenzene: ^1H NMR ($CDCl_2$) δ 7.28 (m, 2H, Ar*H*), 7.18 (m, 3H, Ar*H*) 5.95 (m, 1H, C*H*), 5.05 (m, 2H, CH_2), 3.38 (d, 2H,

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ArCH_2); ^{13}C NMR δ 140.9, 129.4, 129.3, 126.9 (Ar), 138.2 (CH), 112.3 (CH_2), 41.6 (ArCH_2).

Attempted Mitsunobu[5] Reduction of 2-Phenethyl Alcohol (Method A). To a solution of 1.45 g (5.5 mmol) of triphenylphosphine and 0.5 mL (3.7 mmol) of 2-phenethanol in 10 mL of dry methylene chloride was added 0.421 g (11 mmol) of sodium borohydride as a solid all at once. To the slurry was added dropwise 0.708 g (4.07 mmol) of diethyl azodicarboxylate dissolved in 5 mL of dry methylene chloride. The slurry was stirred at room temperature for 24 h whereupon TLC indicated that only starting materials were present. The slurry was then stirred at reflux for an additional 96 h, whereupon TLC indicated that only starting materials were present and the reaction was discontinued.

Method B. To a solution of 1.45 g (5.5 mmol) of triphenylphosphine and 0.708 g (4.07 mmol) of diethyl azodicarboxylate in 10 mL of dry methylene chloride was added dropwise a solution of 0.5 mL (3.7 mmol) of 2-phenethyl alcohol in 5 mL of dry methylene chloride. After 15 min a solution of 0.964 g (11 mmol) of tetra-*n*-butylammonium borohydride in 5 mL of dry methylene chloride was added dropwise. The mixture was stirred at room temperature for 24 h whereupon TLC indicated that only starting materials were present. The mixture was then stirred at reflux for an additional 96 h, whereupon TLC indicated that only starting materials were present and the reaction was discontinued.

Borane-Triphenylphosphine Complex and Menthol. To a solution of 5.56 g (20 mmol) of triphenylphosphine oxide in 30 mL of dry methylene chloride at 0 °C was added dropwise a solution of 1.57 mL (10 mmol) of triflic anhydride in 30 mL of dry methylene chloride. After 15 min when the precipitate appeared, s solution of 1.56 g (10 mmol) of menthol in 10 mL of dry methylene chloride was added and the precipitate vanished in 5 min. An amount of 1.5 g (40 mmol) of sodium borohydride was added as a solid all at once and the slurry was stirred at room temperature for 4.5 h. The mixture was washed twice with 1 N HCl and then water and brine and dried over $MgSO_4$. The resulting oil was purified by column chromatography (CH_2Cl_2) to yield 220 mg (80%) of borane–triphenylphosphine complex and 1.45 g (93%) menthol. No reduced product was obtained. Borane–triphenylphosphine complex: IR[6] (CH_2Cl_2) 2480, 2380, 1104, 1027 cm^{-1}; mp 187–189 °C (lit.[7] 189–191 °C).

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