CHEMISTRY LETTERS, pp. 1657-1660, 1981.

APPLICATION OF THE COMBINATION OF SODIUM BISULFITE AS A PROTECTIVE REAGENT AND SOLID SUPPORTS IN THE SELECTIVE REDUCTION OF 4-ACETYLBENZALDEHYDE WITH DIBORANE

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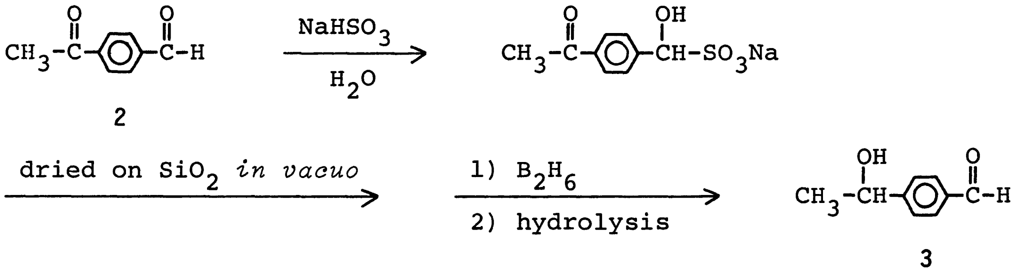
4-Acetylbenzaldehyde (2) has been selectively reduced by using a combination of protective group and solid supports. The formyl group of 2 was protected by addition of sodium bisulfite. The adduct, supported on silica gel, was then selectively reduced to 4-(1-hydroxyethyl)benzaldehyde with diborane.

Sodium bisulfite (1) reacts with unhindered ketones or aldehydes to give bisulfite-addition products. It shows unique reactivity for the carbonyl groups, *e.g.* it gives an adduct with cycloheptanone but not with cyclooctanone.1) Because of limited stability of the adduct, sodium bisulfite is usually utilized only for separation or identification of carbonyl compounds and has not been used as a protective reagent. However, the adducts are stable in aqueous solution or in the form of solid crystals. Further, in aqueous solution the concentration of the product is determined by the equilibrium and this sometimes causes inadequate protection of the carbonyl group (the last row of Table 1). In such a case it may be possible to use the adduct as a solid. Recently, solid adsorbents have been used for selective reactions in organic syntheses.2) Examples are seen in the selective protection of carboxyl groups3) and in the selective oxidation of primary amines and alkyl hydrogen succinates.4)



An attempt to utilize a combination of protective group and solid support for selective reaction was undertaken. Reduction of 4-acetylbenzaldehyde (2),5) which has a formyl and an acetyl group, with diborane, which can only be made use of in an anhydrous system, was chosen as the first representative of this type of reaction involving a solid support and a protective reagent.

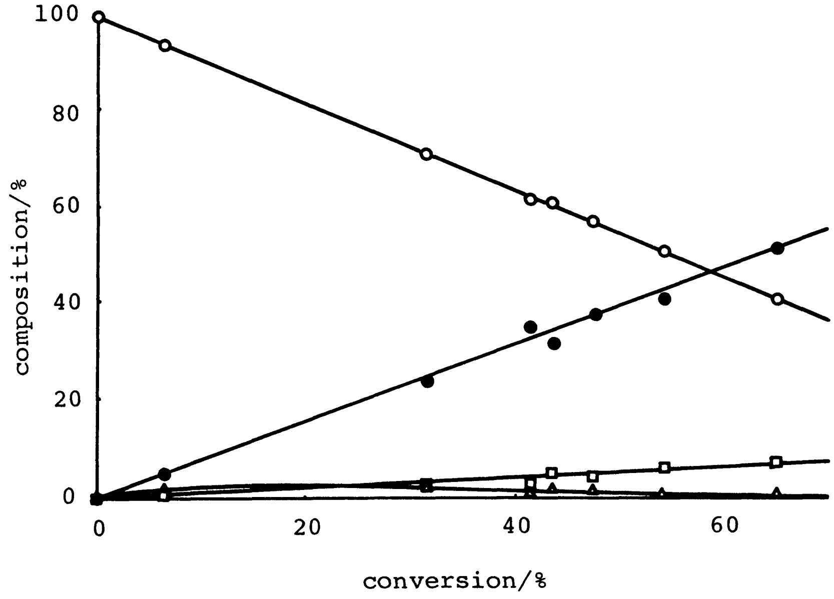


Fig. 1. The reaction profile of heterogeneous reduction of adduct of 1 and 2 on silica gel. The reactions were conducted under molar ratio of 1 to 2 (○), 2 to 1, and wight ratio of combined amount of 1 and 2 to SiO_2, 1 to 10, at 0°C; 3 (●), 4 (△), 5 (□).

Typically, 2 was added to an aqueous solution of 1 and mixed well for 1 hour to produce the adduct. Then an appropriate amount of silica gel (Table 1) was added to the solution and the water was evaporated *in vacuo* at 60°C. Some of 2 was lost in the evacuation procedure and the recovery of 2 from the adduct adsorbed onto the support was 76%. To a packed column of the dried solid a calculated amount of diborane was introduced in a stream of nitrogen at 0°C. The hydroborated adduct was decomposed by the addition of an aqueous solution of sodium hydroxide and the products were extracted with benzene. After concentrating the extract *in vacuo*, the residue was analyzed by g.l.c. The products 4-(1-hydroxyethyl)benzaldehyde (3),6) 4-acetylbenzyl alcohol (4),7) and 1-(4-hydroxymethylphenyl)ethanol (5) were obtained almost quantitatively with less than 2% of side reaction products. Selectivity for the formation of 3 was 70 to 93%.

A plot of the composition of the products against the conversion of the reactant is shown in Fig. 1. The results show that 1 is an effective protective reagent for the formyl group in this reaction. At lower conversions of 2, comparable amounts of 3, 4, and 5 were observed. The product 4 and most of 5 are considered to result from 2 which was not protected.

Table 1. Selective formation of 4-(1-hydroxyethyl)benzaldehyde 3.[a)]

Amount of $NaHSO_3$ 1[b)]	Adsorbent	Amount of adsorbent[c)]	Selectivity for 3/%[d)]
0.5	SiO_2	10	66
1	SiO_2	10	80
2	SiO_2	10	87
5	SiO_2	5	93
5	SiO_2	10	86
5	SiO_2	50	70
5	Al_2O_3	10	77
0	none[e)]	-	0.0
0	SiO_2	10	1.1
5	none[f)]	-	27

[a)] The reactions were conducted *ca.* 5 mg of 2 at 0°C. The products were identified with authentic samples synthesized independently. [b)] Molar ratio relative to 2. [c)] Weight ratio to combined amount of 1 and 2. [d)] Selectivity, {3/(3+4+5)} × 100, was calculated at *ca.* 60% conversion of 2. [e)] Homogeneous reaction in diglyme. [f)] Reduction with sodium borohydride in aqueous solution.

The effect of the amount of 1 and solid support on selectivity for the formation of 3 was examined and the results are shown in Table 1. It was found that selectivity for 3 decreases with decreasing amounts of 1. On the other hand, the selectivity for 3 also decreases with increasing amounts of the solid support. These results are explainable on the basis of the equilibrium between 1, 2, and the adduct, where the amount of the adduct decreases with increasing dilution with water or with increasing amount of the solid adsorbent.

Instead of silica gel, alumina also gave reasonably good results. To confirm the lower reactivity of the acetyl group in comparison with the reactivity of the formyl group, 2 was reduced both in diglyme and on the surface of silica gel without using 1. Table 1 shows that practically all of the formyl group reacted and the acetyl group was intact in both cases. It also shows that selectivity for 3 was low in the reduction of the adduct with sodium borohydride in aqueous solution without using adsorbent.

The adduct is stable only in aqueous neutral solution and in the form of crystals. In the former case diborane is decomposed by water and in the latter case only the surface of the solid adduct crystal may become reduced by diborane gas. Thus, by using the combination of 1 and solid support, product 3 may be obtained selectively by the reduction of 2 followed by hydrolysis.

Such a combination seems possible not only for formyl-acetyl groups, but also in carbonyl-carbonyl groups.1) Another possibility could involve a pair of hindered and unhindered aliphatic ketones.8)

The authors are indebted to Miss Michiko Shinzawa of Tokyo Gakugei University for assisting in the experiments and to Professor Frederic I. Tsuji of the University of California, San Diego, for linguistic comments.

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6) This compound was identified with the sample obtained by independent synthesis as below. First, 2-(4-acetylphenyl)-1,3-dioxolane was prepared by acid-catalyzed condensation of 1 with ethylene glycol: bp 160°C/7 mmHg, mp 50°C and 174°C (semicarbazone); IR (neat) ν=1684 cm^{-1} (C=O); PMR ($CDCl_3$) δ=2.60 (3H, s, CH_3), 4.08 (4H, s, CH_2), 5.83 (1H, s, CH), and 7.52-8.01 (4H, m, aromatic); MS (80 ev), *m/e* (rel intensity), 192 (10), 191 (37), 177 (3), 149 (45), 105 (100), and 43 (74). Then 3 was obtained by the reduction of the acetal with sodium borohydride followed by the hydrolysis: bp 143-4°C/6.5 mmHg, mp 163°C (semicarbazone); IR (neat) ν=3420 (O-H) and 1694 cm^{-1} (C=O); PMR ($CDCl_3$) δ=1.46 (3H, d, J=6.4 H_z, CH_3), 2.55 (1H, s, OH), 4.98 (1H, q, J=6.4 H_z, CH), 7.42-8.11 (4H, m, aromatic), 9.99 (1H, s, CHO); MS (80 eV), *m/e* (rel intensity), 150 (1), 149 (1), 135 (44), 133 (9), 121 (3), 107 (62), 79 (100), 43 (69). These two compounds gave reasonable values in elemental analyses.

7) 4; mp 50°C (lit., 54°C; L. Schmid, W. Swoboda, and M. Wichtl, *Monatsh. Chem.*, 83, 185 (1952).

8) See, for example; L. F. Fieser and M. Fieser, "Reagents for Organic Synthesis," John Wiley and Sons, Inc., New York (1967), p. 1047; *id*, "Textbook of Organic Chemistry," D. C. Heath and Company, Boston (1950), p. 198.

(Received September 9, 1981)