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CHEMOSELECTIVE REDUCTION OF ALDEHYDES WITH TETRA-n-BUTYLAMMONIUM TRIACETOXYBOROHYDRIDE[1]

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Summary: Aldehydes, but not ketones, are smoothly reduced to alcohols by tetra-n-butylammonium triacetoxyborohydride in refluxing benzene.

The chemoselective reduction of aldehydes to primary alcohols, in the presence of ketones, has received a great deal of attention and several methodologies have resulted.[2]

Several years ago we reported[3] that sodium triacetoxyborohydride ($NaBH(OAc)_3$) in refluxing benzene is useful[4] in this regard and, in fact, exhibits excellent aldehyde chemoselectivity even in the presence of excess reagent. However, since the preparation of this reagent involved treating a solid suspension of sodium borohydride in benzene with acetic acid (3.25 equiv.) followed by brief refluxing, it seemed possible that other borohydride species[5] could be present (i.e., BH_3OAc^-, $BH_2(OAc)_2^-$, $B(OAc)_4^-$) and that this, coupled with possible heat-induced decomposition and/or disproportionation during preparation, would obscure the true chemoselectivity of the relatively labile $BH(OAc)_3^-$ ion. Therefore, we have investigated the generation of this species from a soluble borohydride reagent under milder conditions in order to circumvent these aforementioned problems. In this paper we describe the generation of tetra-n-butylammonium triacetoxyborohydride - prepared *in situ* from dichloromethane soluble tetra-n-butylammonium borohydride[6] - and its use as a chemoselective reducing agent.

The results of the treatment of a 1:1 mixture of various alkehydes and ketones with $n\text{-}Bu_4NBH(OAc)_3$ are summarized in the Table. The most striking observation is that even with excess reagent in refluxing benzene for 24 h there is complete reduction of the aldehyde but virtually no reduction of the ketone (analysis by ^1H NMR spectroscopy[7]). Only the unusually reactive ketone 4-*tert*-butylcyclohexanone is affected under these conditions, being slowly reduced to a mixture of *cis*- and *trans*-4-*tert*-butylcyclohexanol in 19% yield after 24 h in refluxing benzene (2.5 hydride equivalents)

Table. Reduction of a 1:1 Mixture of Aldehyde and Ketone by Tetra-n-butylammonium Triacetoxyborohydride in Benzene (80°C, 24 h)[a]

Exp	Aldehyde	Ketone	Yield of Primary Alcohol, %[b]	Yield of Recovered Ketone, %[c]
1	benzaldehyde	acetophenone	95	96
2	phenylacetaldehyde	dibenzylketone	96	94
3	p-methoxybenzaldehyde	acetophenone	95	99
4	benzaldehyde	benzophenone	90	94
5	phenylacetaldehyde	2-heptanone	92	96
6	2,6-dichlorobenzaldehyde	acetophenone	80[d]	92
7	mesitaldehyde	acetophenone	87[e]	96

[a]Initial concentrations were 0.024M ketone, 0.024M aldehyde, and 0.096M n-$Bu_4NBH(OAc)_3$, except in exp. 3 where the borohydride concentration was 0.146M.

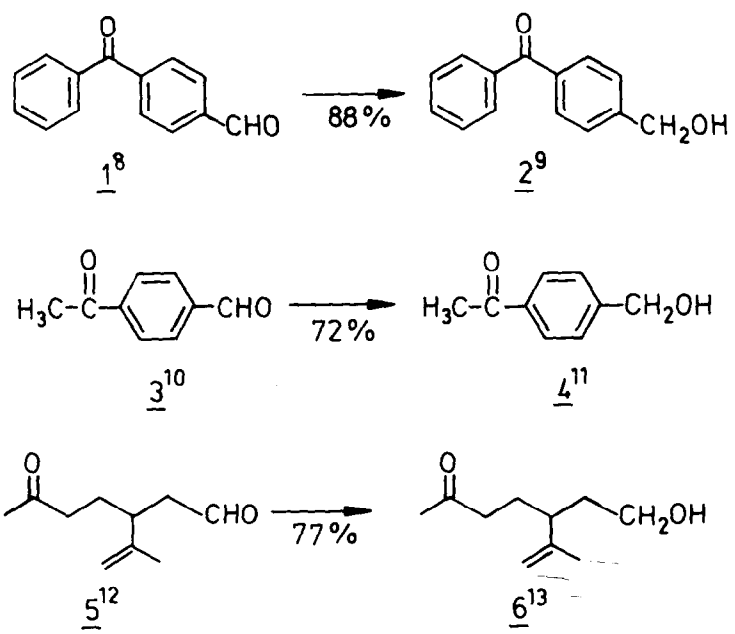
[b]Yield refers to isolated product (column chromatography); identified by ^1H NMR.

[c]Yield refers to isolated ketone (column chromatography).

[d]Mp 95-97°.

[e]Mp 85-87°.

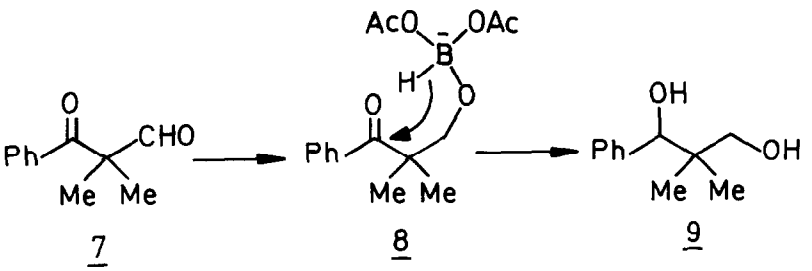
We have also examined several ketoaldehydes (1, 3, 5) and in each case the hydroxyketone (2, 4, 6) is obtained in good yield.



1[8] 2[9] 3[10] 4[11] 5[12] 6[13]

As expected from the work of Raber[6], the reaction of ketoaldehyde 1 with n-Bu_4NBH_4 (one equiv) is nonchemoselective and gives a mixture of 2, the corresponding hydroxyaldehyde, and recovered 1. With excess n-Bu_4NBH_4 1 is transformed into the expected diol[14] (65% yield).

Interestingly, ketoaldehyde 7[15] gave diol 9[16] (80% yield) on treatment with n-$Bu_4NBH(OAc)_3$, presumably the result of intramolecular hydride delivery from intermediate 8. A similar example of ketone reduction in a β-hydroxyketone by $NaBH(OAc)_3$, via intramolecular hydride delivery, has recently been reported.[17]



7 8 9

In summary, it seems evident that the chemoselectivity of the $BH(OAc)_3^-$ ion in aldehyde vs. ketone reductions is even greater than originally reported[3], assuming that the counterion plays no role in these reactions.[6b] Moreover, the simplicity of this aldehyde reduction procedure and the availability[18] of n-Bu_4NBH_4 makes this methodology extremely attractive and an excellent alternative to the existing methods for aldehyde selective reduction.[2]

Representative Procedure. To a magnetically stirred solution of tetra-n-butylammonium borohydride (2.56 g, 0.010 mol) in benzene (50 ml) and dichloromethane (5 ml) at 20°C under nitrogen was added dropwise over 5 min a solution of acetic acid (1.70 ml, 0.030 mol) in benzene (10 ml). This solution was stirred at 20°C for 1 h to complete formation of tetra-n-butylammonium triacetoxyborohydride. The solution was heated to 75-80°C and then treated in one portion with a solution of 4-benzoylbenzaldehyde (1)(0.42 g, 0.0020 mol) in benzene (10 ml). The mixture was refluxed for 24 h and then processed by pouring into water, basifying with sodium hydroxide, and extracting with ether. The organic layer was washed with water, dried (Na_2SO_4), and concentrated in vacuo to afford a yellow oil. Flash chromatography (silica gel) gave 0.37 g (88%) of 4-benzoylbenzyl alcohol (2)[9].

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References and Notes

1. This paper is Part XII in the series "Reactions of Borohydride in Acidic Media". For Part XI, see G.W. Gribble and S.W. Wright, Heterocycles, 19, 229 (1982).

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K. Kikuchi, H. Sugiyama, and S. Seto, Tetrahedron Lett., 263 (1977); (e) $(CH_3)_2CHOH/Al_2O_3$: G.H. Posner, A.W. Runquist, and M.J. Chapdelaine, J. Org. Chem., 42, 1202 (1977); (f) 9-BBN/pyridine: H.C. Brown and S.U. Kulkarni, J. Org. Chem., 42, 4169 (1977); (g) BH_3/LiCl: N.M. Yoon and J.S. Cha, J. Korean Chem. Soc., 22, 259 (1978); (h) n-Bu_3SnH/silica gel: N.Y.M. Fung, P. de/Mayo, J.H. Schauble, and A.C. Weedon, J. Org. Chem., 43, 3977 (1978); (i) B-siamyl-9-BBN: M.M. Midland and A. Tramontano, J. Org. Chem., 43, 1470 (1978); (j) $LiBH_4$/mol sieve: P.A. Risbood and D.M. Ruthven, J. Org. Chem., 44, 3969 (1979); (k) BH_3/RNH_2: G.C. Andrews, Tetrahedron Lett., 21, 697 (1980); (l) Et_4NBH_4: T.N. Sorrell and P.S. Pearlman, Tetrahedron Lett., 21, 3963 (1980); (m) $(Ph_3P)_2CuBH_4$: G.W.J. Fleet and P.J.C. Harding, Tetrahedron Lett., 22, 675 (1981); (n) $EtCH(OMgBr)_2$: J.H. Babler and B.J. Invergo, Tetrahedron Lett., 22, 621 (1981); (o) $NaBH(OAr)_3$: S. Yamaguchi, K. Kabuto, and F. Yasuhara, Chem. Lett. 461 (1981); (p) NaOCHO: J.H. Babler and S.J. Sarussi, J. Org. Chem. 46, 3367 (1981); (q) $Li(Et_3CO)_3$ AlH: S. Krishnamurthy, J. Org. Chem., 46, 4628 (1981).

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6. For the development of this reagent, see (a) D.J. Raber and W.C. Guida, J. Org. Chem., 41, 690 (1976); (b) D.J. Raber, W.C. Guida, and D.C. Shoenberger, Tetrahedron Lett., 22, 5107 (1981).

7. Known mixtures of the ketone reduction product and the aldehyde reduction product indicated that $\geq$1% ketone reduction could have been detected by ^{1}H NMR.

8. Prepared from 4-methylbenzophenone using the general procedure of S.V. Lieberman and R. Connor, Org. Syn. Coll. Vol.III, 441 (1943); mp 62-65° (Lit. mp 64°: P. Bourcet, Bull. Soc. Chem. Fr., 15, 945 (1896)).

9. Mp 61-64°; ^{1}H NMR($CDCl_3$): δ 3.6 (m, 1 H), 4.7 (s, 2 H), 7.5 (m, 9 H); IR ($CHCl_3$) 3630, 3470, 1660 cm^{-1}; ^{13}C NMR($CDCl_3$): δ 64.4, 126.2, 128.1, 129.8, 130.2, 132.2, 136.5, 137.5, 145.6, 196.4.

10. Prepared from 4-bromoacetophenone by the sequence: (a) CuCN, (b) ketalization, (c) DIBAL, (d) hydrolysis; oil.

11. Mp 51-54°C; ^{1}H NMR ($CDCl_3$) δ 2.6 (s, 3 H), 2.95 (m, 1 H), 4.75 (s, 2 H), 7.7 (m, 4 H); IR ($CHCl_3$) 3640, 1690 cm^{-1}; ^{13}C NMR ($CDCl_3$) δ 26.5, 64.4, 126.5, 128.4, 136.2, 146.1, 197.7; Anal. Calcd for $C_9H_{10}O_2$: C, 72.00; H, 6.66. Found: C, 72.04; H, 6.73.

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13. Oil; ^{1}H NMR ($CDCl_3$) δ 1.6 (m, 7 H), 2.1 (s, 3 H), 2.4 (m, 3 H), 3.5 (t, 3 H), 4.75 (s, 2 H), ^{13}C NMR ($CDCl_3$) δ 17.5, 26.6, 29.9, 36.0, 41.3, 43.5, 61.0, 112.6, 146.5, 208.7; IR (neat) 3420, 1705 cm^{-1}; Anal. Calcd for $C_{10}H_{18}O_2$: C,70.49; H, 10.57. Found: C, 69.75; H, 10.55; ms m/e 170.1319 (M+, calcd 170.1307).

14. Mp 103-106°C; ^{1}H NMR ($CDCl_3$) δ 1.8 (m, 1 H), 2.4 (m, 1 H), 4.65 (s, 2 H), 5.9 (d, 1 H), 7.3 (s, 9 H); Anal. Calcd for $C_{14}H_{14}O_2$: C, 78.50; H, 6.54. Found C, 78.32, H, 6.60.

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