Tetrahedron Letters,Vol.28,No.40,pp 4725-4728,1987 0040-4039/87 $3.00 + .00
Printed in Great Britain Pergamon Journals Ltd.

SELECTIVE REDUCTION OF KETONES WITH SODIUM BOROHYDRIDE-ACETIC ACID

Tuula E.A. Nieminen and Tapio A. Hase
University of Helsinki, Department of Chemistry
Vuorikatu 20, SF-00100 Helsinki, Finland

Summary: Aliphatic ketones, and aromatic ketones having o-hydroxy or o-amino substituents are reduced rapidly to the alcohols by $NaBH_4$ and acetic acid; other types of ketones react much more slowly.

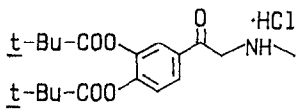
$NaBH_4$ reacts with glacial acetic acid to form acetoxyborohydrides.[1-3] Presumably, adjusting the stoichiometry will determine the number of acetoxy groups but all acetoxyborohydrides have by no means been fully characterized.

$$NaBH_4 \xrightarrow{HOAc} NaBH_3(OAc) \xrightarrow{HOAc} NaBH_2(OAc)_2 \xrightarrow{HOAc} NaBH(OAc)_3 \xrightarrow{HOAc} NaB(OAc)_4$$

Mono-, di- and triacetoxyborohydrides are apparently formed rapidly even at room temperature, while the last hydride is released very slowly.[2,4] $NaBH(OAc)_3$[4] and $NaBH_3(OAc)$[5,6] have been isolated and their IR spectra measured, and the first-mentioned has quite recently become commercially available.[7] Some chiral amine mono-, di- and triacyloxyborohydride complexes have also been isolated and analysed with IR, NMR and mass spectroscopy.[8]

$NaBH_4$ in the presence of excess of acetic acid has been used for reductions of enamines, imines, vinylogous carbamates, aromatic and aliphatic α,β-unsaturated tosylhydrazones, pyrylium salts[9], for reduction or reductive N-alkylation of amines, oximes[10] and nitrogen containing heterocycles.[2] Various reactions have also been run in nonpolar solvents (e.g. THF) using one or three mole equivalents of acetic acid relative to $NaBH_4$. Reactions corresponding to use of $NaBH_2(OAc)_2$ have not been reported. One equivalent of HOAc (i.e. $NaBH_3OAc$) has been used for hydroboration of alkenes and for reduction of amides and carbamates.[2] Three mole equivalents [i.e., $NaBH(OAc)_3$] have been used for reduction of cyclic imines and aldehydes in the presence of ketones.[2]

Aldehydes and especially ketones are reduced more slowly to alcohols with $NaBH_4$ in glacial acetic acid than in alcoholic solutions. Aromatic ketones such as acetophenone and benzophenone are not reduced completely with $NaBH_4$ in HOAc. Chemoselective reduction of aldehydes in the presence of ketones using $NaBH(OAc)_3$ is therefore feasible.[2] An amino group α to carbonyl has also proved advantageous in reduction with $NaBH_4$ in HOAc,[11] 1 being reduced to the corresponding aminoalcohol in good yield:



1

Some diastereoselective reductions of β-hydroxyketones have been reported with the $NaBH_4$/HOAc-system.[12,13,14] Cyclic imines have been reduced with chiral sodium acyloxyborohydrides to optically active amines in 55-60% yield.[8] Very recently, aliphatic β-ketols were shown to be reduced selectively to the anti diols with tetramethylammonium triacetoxyborohydride.[15]

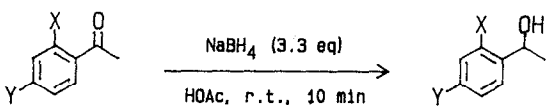
We now wish to report a new type of selective reduction of ketones to the corresponding alcohols using $NaBH_4$ in glacial acetic acid solvent, or $NaBH_4$ in THF in the presence of stoichiometric amounts of acetic acid.

Reductions in glacial acetic acid

General procedure: 310 mg $NaBH_4$ (8.2 mmole) is added slowly with cooling to the ketone (2.5 mmol) in 10 ml of glacial acetic acid, the reaction temperature being maintained at 16-21 °C. After ten minutes the reduction is interrupted by adding 10 ml of water, the mixture neutralized with aqueous $NaHCO_3$ and the reaction product isolated by extraction with ether, drying and evaporation, and identified by the usual spectroscopic methods.

Aldehydes such as vanillin and aliphatic ketones such as cyclohexanone are reduced rapidly and completely with $NaBH_4$ in HOAc at room temperature, whereas aralkylketones such as acetophenone react much more slowly. Diarylketones such as benzophenone are not reduced at all even with extended reaction times.

Table 1: Reduction of substituted acetophenones



X	Y	conversion (%) by NMR
H	H	23
OH	H	100
NMe_2	H	100
NH_2	H	88
OMe	H	18
Br	H	18
H	OH	12
H	NMe_2	12
H	NH_2	23
H	Br	20
m-NH_2		36
3,5-dihydroxy		0

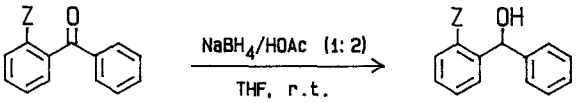
As seen in Table 1 acetophenone is reduced with this system to the the corresponding alcohol with only 23% conversion, and in 24 hours not more than 60% of acetophenone was reduced. Butyrophenone is essentially stable towards $NaBH_4$ in acetic acid. However, aralkylketones carrying a hydroxy group in the ortho-position undergo a rapid and complete reduction. Similarly, o-(N,N-dimethylamino)acetophenone was cleanly and rapidly reduced to the corresponding alcohol. o-Aminoacetophenone was reduced in 88% conversion in ten minutes with $NaBH_4$ in HOAc. Further reduction of the remaining ketone was inefficient and only caused the appearance of numerous by-products.

Reductions in THF using stoichiometric amounts of acetic acid

Reducing o-aminobenzophenone with $NaBH_4$ in acetic acid gave considerable amounts of by-products in addition to the expected alcohol. However, reduction with $NaBH_4$ in THF in the presence of 2 equivalents of acetic acid proceeds smoothly to give the alcohol in essentially quantitative yield (Table 2). Similarly, o-hydroxybenzophenone is readily reduced whereas other the ortho-substituents are less effective or do not promote the reaction at all.

General procedure: Acetic acid (18 mmol) is added slowly with cooling to $NaBH_4$ (9 mmol) in 10 ml of THF. After the evolution of hydrogen has ceased the ketone (45 mmol) is added at room temperature. After complete disappearance (TLC) of the starting material the reaction mixture is worked up as before.

Table 2: Reduction of o-substituted benzophenones

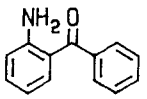
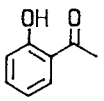
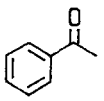


Z	time for complete reduction
H	60 h
OH	5 min
NH_2	1 h
NHMe	3 h
OMe	30 h

In summary, we have shown that aralkyl or diaryl ketones carrying ortho hydroxy or ortho-amino substituents can be rapidly and cleanly reduced to the alcohols using one of the $NaBH_4$/HOAc reagent systems. Other ortho substituted ketones, or ketones having hydroxy or amino functions elsewhere in the ring are relatively stable towards reduction. It is possible that the hydroxyketones react by first forming a borate ester, facilitating the delivery of a hydride ion via a six-membered transition state. This is in keeping with the failure of ortho halo or alkoxy groups to promote the reaction, or of hydroxy groups at sites other than ortho. Amino groups apparently react via the nitrogen lone electron pair to form a N→B coordination complex, again furnishing favorable geometry for the delivery of H^-.

Regarding the identity of the reducing species in our reactions, we only have circumstatial evidence to suggest that in acetic acid solvent, the reducing agents are $NaBH_3(OAc)$ and $NaBH_2(OAc)_2$. As for the reductions in THF using the 1:2 $NaBH_4$:HOAc reagent combination, we assume that the reducing species is the one that corresponds to this stoichiometry, namely $NaBH_2(OAc)_2$. These arguments are supported by the data seen in Table 3, showing that reductions using $NaBH(OAc)_3$ proceed much more slowly than the same reductions with $NaBH_3(OAc)$ or $NaBH_2(OAc)_2$. Especially reduction of ortho-aminobenzophenone or the parent acetophenone is practically at standstill in THF using the 1:3 reagent ratio which corresponds to $NaBH(OAc)_3$, known to be ineffective in reductions of aromatic ketones.

Table 3: The effect of stoichiometry on the reduction of ketones in THF.

ketone	$NaBH_4$:HOAc	time for complete reduction
	1 : 1 or 2 1 : 3	1 h 12 days
	1 : 2 1 : 3	2 min 10–15 min
	1 : 1 or 2 1 : 3	1,5 h < 10% reduction in 2 days

1. G.W. Gribble, Eastman Org. Chem. Bull. 51 (1979) 1.
2. G.W. Gribble and C.F. Nutaitis, Org. Prep. Proced. Int. 17 (1985) 317.
3. B.T. Cho, Synth. Commun. 15 (1985) 917.
4. P. Marchini, G. Liso and A. Reho, J. Org. Chem. 40 (1975) 3453.
5. T. Reetz, J. Am. Chem. Soc. 82 (1960) 5039.
6. P.G. Egan and K.W. Morse, Polyhedron 1 (1982) 299.
7. Aldrich Chemical Co., 31,639-3.
8. K. Yamada, M. Takeda and T. Iwakuma, J. Chem. Soc. Perkin Trans. 1 (1983) 265.
9. T-S. Balaban and A.T. Balaban, Tetrahedron Lett. 28 (1987) 1341.
10. G.W. Gribble, Ventron Alembic No 8 (1977).
11. Finn. Pat. 61474 (1982).
12. A.K. Saksena and P. Mangiaracina, Tetrahedron Lett. 24 (1983) 273.
13. M.D. Turnbull, G. Hatter and D.E. Ledgerwood, Tetrahedron Lett. 25 (1984) 5449.
14. D.A. Evans and M. DiMare, J. Am. Chem. Soc. 108 (1986) 2476.
15. D.A. Evans and K.T. Chapman, Tetrahedron Lett. 27 (1986) 5939.

(Received in UK 23 June 1987)