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REDUCTIVE AMINATION OF ALDEHYDES AND KETONES BY USING SODIUM TRIACETOXYBOROHYDRIDE[1]

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Summary: Sodium triacetoxyborohydride is a reagent of choice in the reductive amination of aldehydes and saturated aliphatic ketones with primary and secondary amines.

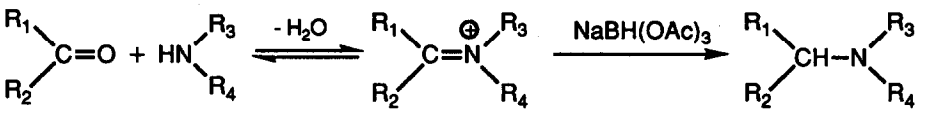
The reductive amination of aldehydes and ketones is one of the most useful reactions in the synthesis of primary, secondary and tertiary amines.[2] The Borch reduction,[3] using sodium cyanoborohydride [$NaBH_3CN$] has been the most popular method to carry out this transformation in recent years. However, in our work, we desired a hydride alternative to this toxic reagent to eliminate any risk of residual cyanide in the product or in the workup waste stream. We selected sodium triacetoxyborohydride [$NaBH(OAc)_3$],[4] a very mild and selective reducing agent.[5] The reagent reduces aldehydes selectively over ketones;[5,6] Gribble had previously shown the potential for its use in reductive amination.[7] In this paper, we report our preliminary work on the scope and limitations of sodium triacetoxyborohydride in the reductive amination of aldehydes and ketones.

Table I shows that a wide variety of aliphatic and cyclic saturated ketones and aldehydes were reductively aminated with primary and secondary amines under the standard conditions in good to excellent yields.[8] The reductive aminations were carried out in either 1,2-dichloroethane (DCE) or tetrahydrofuran (THF). In general, the mixture of the carbonyl compound (10 mmol) and the amine (10-11 mmol) in DCE or THF (30-40 mL) was treated with sodium triacetoxyborohydride (14-15 mmol) under a nitrogen atmosphere at room temperature. With most ketones and with some aldehydes, acetic acid (10 mmol) was added to the mixture. The progress of the reaction was followed by GC and GC/MS analysis. In general, most of the reactions carried out in DCE were faster than those carried out in THF, and in both solvents, addition of one (or more) equivalent (s) of acetic acid (AcOH) accelerated the reaction.[9]

Generally, with the same ketone, primary aliphatic amines reacted faster than primary aromatic and secondary aliphatic amines (Table I, entries 2 vs. 3 and 11 vs. 15). Among the secondary amines, cyclic amines such as morpholine reacted faster than acyclic amines such as diethylamine (Table I, entry 5 vs. 6) while sterically hindered diisopropylamine did not react even after days (Table I, entry 7). Aromatic and α,β-unsaturated ketones, on the other hand, reacted very slowly (Table I, entries 24, 25 and 26).

In competition experiments, we found that an aliphatic ketone reacted, selectively and quantitatively, in the presence of an aromatic or α,β-unsaturated ketone. Thus, competitive reaction

TABLE I: REDUCTIVE AMINATION OF ALDEHYDES AND KETONES USING SODIUM TRIACETOXYBOROHYDRIDE



entry	Carbonyl Compound	Amine	method[a]	time (h)	product % yield
1	Cycloheptanone	1-Propylamine	III	3	88 (HCl)
2	2-Heptanone	Cyclohexylamine	II	24	84 (ox)[b]
3	2-Heptanone	Aniline	IV	96	89 (ox)[b]
4	2-Heptanone	Aniline	I	96	74
5	2-Heptanone	Morpholine	I	27	73 (HCl)
6	2-Heptanone	Diethylamine	I	192	44 (HCl)
7	Cycloheptanone	Diisopropylamine	I, II	96	N R[c]
8	Cyclohexanedione monoketal[d]	Piperidine	III	1.25	85
9	Cyclohexanedione monoketal[d]	Benzylamine	III	0.3	92
11	Norcamphor	Benzylamine	IV	6	95[e]
12	Benzaldehyde	*endo*-2-Aminonorbornane	IV	0.5	85 (HCl)[e]
13	Norcamphor	Aniline	I	48	75 (HCl)[e]
14	Norcamphor	Aniline	III	6	76 (HCl)[e]
15	Norcamphor	Diethylamine	III	96	79 (ox)[e]
16	4-*t*-Butylcyclohexanone	Pyrrolidine	IV	0.17	98[f]
17	4-*t*-Butylcyclohexanone	Isopropylamine	III	0.5	98[g]
18	Cyclohexane carboxaldehyde	Morpholine	II	2	74
19	Cyclohexane carboxaldehyde	Diethylamine	IV	0.5	84 (HCl)
20	Cyclohexane carboxaldehyde	Diisopropylamine	III	3	41 (HCl)
21	Benzaldehyde	*t*-Butylamine	III	3	95
22	*m*-Anisaldehyde	Aniline	III	0.3	95 (HCl)
23	*m*-Anisaldehyde	Morpholine	II	6	88
24	Acetophenone	Benzylamine	III	240	55[h]
25	Acetophenone	Cyclohexylamine	I, III	24	15[h]
26	1-Acetylcyclohexene	Morpholine	II	96	10[h]

a) methods; I: THF, AcOH (1 equiv.), $NaBH(OAc)_3$ (1.3-1.5 equiv.); II: THF, $NaBH(OAc)_3$ (1.3-1.5 equiv.); III: DCE, AcOH (1 equiv.), $NaBH(OAc)_3$ (1.3-1.5 equiv.), IV: DCE, $NaBH(OAc)_3$ (1.3-1.5 equiv.).
b) ox = oxalate. c) no reaction . d) 1,4-cyclohexanedione monoethylene ketal. e) endo product f) about 3 : 1 ratio of axial/equatorial. g) about 4 : 1 ratio of axial/equatorial. h) yield was determined by GC.

of 1-acetylcyclohexene and acetylcyclohexane (1:1) with benzylamine for 1h led to a 98% yield of N-(1-cyclohexylethyl)benzylamine and recovered 1-acetylcyclohexene; competitive reaction of acetophenone and cyclohexanone (1:1) with benzyl amine for 4h led to a 85% isolated yield of N-cyclohexyl benzylamine and unreacted acetophenone. In these cases, there was no detectable reaction with the aromatic or unsaturated ketone, except for the formation of trace amounts of their imines.

The reaction conditions tolerate the presence of an acid sensitive group such as a ketal. Thus, the reductive amination of cyclohexanedione monoethylene ketal with benzylamine and piperidine in the presence of one mole of acetic acid afforded isolated yields of 92% and 85% of the corresponding amines (Table I, entries 8 and 9).

The reductive amination of norcamphor led to the exclusive formation of the *endo* products, probably from an *exo* attack by the hydride reagent on an intermediate imine. The predominance of the *endo* product was confirmed by reductive amination of benzaldehyde with *endo*-2-aminonorbornane (Table I, entry 11) which produced a product identical to that obtained from reductive amination of norcamphor with benzylamine (Table I, entry 12). Reductive amination of 4-*tert*-butyl cyclohexanone with pyrrolidine and isopropylamine occurred with a moderate diastereoselectivity towards the thermodynamically less favored *cis* products resulting from equatorial attack by the hydride reagent on the intermediate imine[10] (Table I, entries 16 and 17).

Unlike ketones, aldehydes can be reduced with sodium triacetoxyborohydride.[4] However, in only one case was the aldehyde reduction noticeable: Table I, entry 20 which involved a reaction with the very sterically hindered diisopropylamine. All others (Table I, entries 12, 18, 19, 21, 22 and 23) resulted in fast and efficient reductive aminations with both primary and secondary amines in reaction times ranging from 20 minutes to 6 hours. In the reactions between aldehydes and primary amines, formation of dialkylated amines can be suppressed by addition of a 10% molar excess of the primary amine.

In representative comparison reactions, sodium triacetoxyborohydride in 1,2-dichloroethane reacted consistently faster, gave better yields and produced fewer side products than sodium cyanoborohydride in methanol when used in reductive amination reactions.[9] So, in conclusion, sodium triacetoxyborohydride is a good alternative to sodium cyanoborohydride; its use eliminates the problem of the residual cyanide in the product and in the waste stream.

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References and Notes:

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5. The mildness of the reagent was attributed to both the steric and the electron withdrawing effects of the acetoxy groups which stabilize the boron-hydrogen bond. Gribble, G. W. *Eastman Organic Chemical Bulletin* **1979**, *51*, No. 1.
6. Triacetoxyborohydrides do not usually reduce aliphatic and aromatic ketones[4] but do reduce β-hydroxyketones selectively to the *trans* 1,3-diols. See for example: (a) Saksena, A. K.; Mangiaracina, P. *Tetrahedron Lett.* **1983**, *24*, 273, (b) Evans, D. A.; Chapman, K. T. *Tetrahedron Lett.* **1986**, *27*, 5939, (c) Evans, D. A.; Chapman, K. T.; Carreira, E. M. *J. Am. Chem. Soc.* **1988**, *110*, 3560.
7. Earlier work by Gribble et al., demonstrated the potential of triacyloxyborohydrides generated from $NaBH_4$ in neat liquid carboxylic acids in reductive aminations involving aromatic amines: (a) Gribble, G. W.; Lord, P. D.; Skotnicki, J.; Dietz, S. E.; Eaton, J. T.; Johnson, J. L. *J. Am. Chem. Soc.* **1974**, *96*, 7812, (b) Gribble, G. W.; Jasinski, J. M.; Pellicone, J. T.; Panetta, J. A. *Synthesis* **1978**, 766.
8. All products showed spectroscopic properties and elemental analyses consistent with their structures.
9. A more detailed account of the comparative rates of reductive aminations with $NaBH(OAc)_3$ in DCE vs. THF, the effect of acetic acid as well as comparisons between $NaBH(OAc)_3$/DCE and $NaBH_3CN$/MeOH reactions will be reported.
10. This result is consistent with an earlier study on reduction of 4-substituted cyclohexanone imines which concluded that bulky hydride reagents attack preferentially from the equatorial side in contrast to small hydride reagents such as $NaBH_4$ and $NaBH_3CN$ which favor the axial approach. See Hutchins, R. O.; Su, W. Y.; Sivakumar, R.; Cistone, F.; Stercho, Y. P. *J. Org. Chem.* **1983**, *43*, 3412.

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