Reduction of Carboxylic Acid Derivatives by BH_4^- in Acidic Dimethyl Sulfoxide[1]

Steven R. Wann, Peter T. Thorsen, and Maurice M. Kreevoy*

Laboratory for Chemical Dynamics, Department of Chemistry, University of Minnesota, Minneapolis, Minnesota 55455

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Carboxylic acid amides of all degrees of substitution, both aliphatic and aromatic, can be reduced to the corresponding primary, secondary, or tertiary amines in good yield by a combination of $NaBH_4$ and CH_3SO_2OH in dimethyl sulfoxide. The procedure also reduces aliphatic carboxylic acids and their esters to primary alcohols, but not conjugated aromatic acids. Crotonic acid is readily reduced to butanol. Isolated double bonds and nitriles also react, but the major products are not those of simple reduction. Michler's ketone is reduced to 4,4'-bis-(dimethylamino)diphenylmethane. The acid probably facilitates the amide reduction by protonating the carbonyl oxygen. The mechanism of the other reductions is less clear. The method does not require an anhydrous solvent, does not involve a hazardous reagent, has somewhat different selectivity than techniques in general use, and may sometimes be the method of choice.

The acid-catalyzed hydrolysis of tetrahydridoborate ion, BH_4^-, in nearly dry dimethyl sulfoxide is slower than that in water by a factor of 10^6.[2] This attenuated rate of acid-catalyzed decomposition allows the use of $NaBH_4$ to effect acid-promoted reductions in Me_2SO that are not possible in hydroxylic solvents, because of the rapid loss of the reagent. For example, vat dyes (highly conjugated ketones) do not react with BH_4^- in alkaline aqueous solution, but are quickly reduced to their leuco forms with $NaBH_4$ in acidic Me_2SO.[3] We now report on the expansion of this reduction system to other functional groups: carboxylic acids, esters, and amides; also the vinylogous urea, 4,4'-bis(dimethylamino)benzophenone (Michler's ketone).

Experimental Section

Materials. Sodium borohydride was a gift of the Ventron Corporation (now Thiokol/Ventron) and was used without further purification. The activity of the reagent was periodically monitored with nicotinamide adenine dinucleotide (NAD^+)[4] and it always proved to be >90% active. Me_2SO (99%+) was purchased from the Aldrich Chemical Co. and used without purification. Water is its only obvious impurity, and yields were unchanged by deliberate addition of 0.02 M or even 1.0 M water to the reaction mixture. Methanesulfonic acid (Aldrich) was distilled under vacuum prior to use [bp 112-114 °C (0.5 mm), lit.[5] bp 167 °C (10 mm)]. All other reagents were purchased from the usual suppliers. They were the best available commercial grades and were used without purification.

Procedure (Amides). To a vented, 100-mL, two-necked flask equipped with a magnetic stirrer were added 16 mmol of amide, 1.61 g (40 mmol) of $NaBH_4$, and 20 mL of Me_2SO. Methanesulfonic acid (3.4 mL, 55 mmol) and 20 mL of Me_2SO were mixed and added dropwise to the reaction mixture by means of an addition funnel over a 30-min period. During this addition the reaction mixture was constantly stirred with a magnetic stirrer. Gas was continually evolved during the addition of acid and a gelatinous substance formed, which dissolved when the acid came to exceed the $NaBH_4$ on a molar basis. At the end of this time, if the reduction product was to be a primary or secondary amine, the reaction mixture was quenched by the addition of 20 mL of 10% NaOH. If the product was to be a tertiary amine, the reaction mixture was kept at 70 °C for 2 h to liberate the product from what appeared, from its NMR spectum, to be a complex with BH_3. After this additional reaction period tertiary amines were isolated in the same way as primary or secondary amines.

Table I. Isolated Yields from Reductions with BH_4^- in Acidic Me_2SO

substrate	product	bp, °C	% yield
$CH_3(CH_2)_4CONH_2$	$CH_3(CH_2)_5NH_2$	bp_{25} 38-40[a]	74
$PhNHCOCH_3$	$PhNHCH_2CH_3$	bp_{15} 90-91[b]	77
$PhCON(CH_3)_2$	$PhCH_2N(CH_3)_2$	bp_{22} 73-77[c]	59
$PhCH_2COOH$	$PhCH_2CH_2OH$	bp_{22} 100-103[d]	87
$(p\text{-}N(CH_3)_2C_6H_4)_2CO$	$(p\text{-}N(CH_3)_2C_6H_4)_2CH_2$	mp 89-90.5[e]	88

[a] Lit. bp_{32} 47.7 °C; Ralston, A. W.; Selby, W. M.; Pool, W. O.; Potts, R. H. *Ind. Eng. Chem.* **1940**, *32*, 1093. [b] Lit. bp_{17} 93-94 °C; Mićović, V. M.; Mihailović, M. L.; *J. Org. Chem.* **1953**, *18*, 1190. [c] Lit. bp_{30} 83-84 °C; King, J. A.; McMillan, F. H. *J. Am. Chem. Soc.*, **1946**, *68*, 1468. [d] Lit. bp_{760} 205-212 °C; Morton, A. A.; Falwell, F. Jr. *J. Am Chem. Soc.* **1938**, *60*, 1429. [e] Lit.[5] mp 89 °C.

After the reaction was quenched, the product was extracted from the reaction mixture with three 10-mL portions of methylene chloride or chloroform. The product solution was then washed with three 10-mL portions of 0.1 M NaOH to remove most residual Me_2SO, and the product was extracted into three 10-mL portions of 10% HCl. Neutralization with 10% NaOH, followed by extraction with three 10-mL portions of methylene chloride, drying over $CaSO_4$, and fractional distillation, afforded the various amines (Table I). In some experiments the amine product was not isolated, but an NMR method was used to determine the yield. In this method, most of the solvent was removed from the final, dried methylene chloride layer by evaporation with a rotary evaporator. The total remaining solution was carefully weighed and a small, accurately weighed portion (~200 mg) was placed in an NMR tube. Carefully weighed quantities of either dimethyl formamide or *s*-trioxane were added to the tubes as intensity standards and peak areas were recorded. Keeping in mind the numbers of equivalent protons giving the signals, product concentrations, and finally yields, were calculated. The percentage yield calculated by the NMR technique was always within ±10% of the isolated yield for those amines in which both the isolation and NMR method were used.

Procedure (Acids and Esters). In a vented, 100-mL, two-necked round-bottomed flask, equipped with a magnetic stirrer, were placed 16 mmol of acid or ester, 1.61 g (40 mmol) of $NaBH_4$, and 20 mL of Me_2SO. A solution of 3.4 mL (55 mmol) of

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Table II. Reduction Yields by NMR Spectroscopy[a]

substrate	% yield
hexanamide	84
acetanilde	79
N,N-dimethylbenzamide	12[b]
N-methyl-2-phenylacetamide	68
ϵ-caprolactam	73
phenylacetic acid	95
acetic acid	93
d-phenylalanine	11[d]
crotonic acid	12[e]
	48[f]
triacetin	42
	98[g]
cyclohexene	10
benzoic acid	n.r.
methyl benzoate	n.r.

[a] All run with 2.5 mol of $NaBH_4$ and 3.5 mol of CH_3SO_3H unless otherwise noted. [b] 1 equiv of $NaBH_4$ was used. [c] 5 equiv of $NaBH_4$ was used. [d] After 25 h of continuous liquid–liquid extraction of the quenched solution with diethyl ether. [e] Based on *n*-butanol obtained by steam distillation. [f] 5 equiv of $NaBH_4$ was used; based on *n*-butanol obtained by steam distillation. [g] 7.5 equiv was used.

methanesulfonic acid in 20 mL of Me_2SO was added to the reaction mixture while stirring vigorously. In one experiment sulfuric acid was used in place of methanesulfonic acid without apparent diminution of yield (Table II). At the end of this time, the reaction mixutre was quenched by the addition of 20 mL of 10% NaOH. The product was extracted from the quenched reaction solution with five 10-mL portions of diethyl ether, which were combined, dried over $CaSO_4$, and distilled to isolate the products. Yields are given in Table II.

For those acids and esters whose reduction product was ethanol, the reaction mixture was partially distilled after quenching and before extraction with ether. Distillation was continued until all the ethanol was removed azeotropically. The yield of ethanol was then determined by applying the NMR method directly to the aqueous distillate.

In the acetic acid reduction, the amount of unreacted acid could also be determined after all the ethanol was removed. This was accomplished by acidification of the reaction mixture with 10% HCl followed by distillation to azeotropically remove acetic acid. When all the acetic acid was removed, a known volume of the distillate was titrated to a phenolphthalein end point with standard NaOH. The sum of the ethanol and acetic acid recovered was always within 10% of theoretical.

Procedure (Michler's Ketone). Michler's ketone (0.53 g, 2 mmol), 0.19 g of $NaBH_4$ (5 mmol), and 3 mL of Me_2SO were combined in a 50-mL three-necked flask. A solution of 0.43 mL of methanesulfonic acid (6.5 mmol) in 3.5 mL of Me_2SO was added over a period of 30 min, while the reaction mixture was being vigorously stirred. A precipitate formed during the addition. When the addition of the acid was complete, 35 mL of 10% NaOH in water was added to neutralize the excess acid and complete the precipitation of the product. Filtration and one recrystallization from ethyl ether gave 0.45 g (1.8 mmol) of 4,4′-bis(dimethylamino)diphenylmethane, mp 89–90.5 °C (lit.[5] mp 89 °C).

Results

If the reaction were governed by eq 1 and 2, 0.5 mol of

$$0.5BH_4^- + RCONR'_2 \rightarrow RCH_2NR'_2 + 0.5BO_2^- \quad (1)$$

$$0.5BH_4^- + RCOOR' \rightarrow 0.25(RCH_2O)_4B^- + 0.25(R'O)_4B^- \quad (2)$$

$NaBH_4$ would be required for each mole of amide, ester, or acid. For the reduction of acetic acid, a detailed survey was made of the effect of reagent quantities and reaction time on the yield. A less complete study was carried out for *N,N*-dimethylbenzamide, and a few observations were made for other compounds. All of these showed that yields

Table III. Reduction of Acetic Acid by BH_4^- in Acidic Me_2SO

mol $NaBH_4$ / mol AcOH	mol CH_3SO_3H / mol AcOH	% yield
2.5	1.25	34
2.5	1.25	46[a]
2.5	1.25	53[b]
2.5	3.5	94
1.25	3.5	17
1.25	1.75	19
1.63	1.75	50
1.03	1.75	11[c]
2.0	2.71	58[c]
2.0	2.71	65
2.5	3.5	96[d]
2.5	3.5	93[e]
5.0	3.5	98

[a] 2 h, 25 °C. [b] 19 h, 70 °C. [c] CH_3SO_3H and CH_3CO_2H are added simultaneously. [d] H_2SO_4 used instead of CH_3SO_3H. [e] 1.0 M H_2O present in reaction solution.

improved with an increasing excess of $NaBH_4$ up to about 2.5 mol per mole of functional group to be reduced. Beyond that level, further improvements were minimal. Part of the additional BH_4^- was wasted in reducing Me_2SO to dimethyl sulfide, which could easily be detected in all our product mixtures, and a substantial part was always wasted in the production of H_2, by direct reaction with the acid. When tertiary amines are produced it is clear that some of the BH_4^- is also wasted by conversion to a form too unreactive to carry out the reduction. It is not known if such as loss also occurs in the other cases. In order to produce a tractable reaction mixture the number of moles of methanesulfonic acid had to exceed those of $NaBH_4$.

Our structural survey showed that aromatic amides as well as aliphatic amides are reduced in good yield. If the amine–boranes are decomposed by holding the reaction mixture at 70 °C for 2 h there is no apparent distinction among unsubstituted, monosubstituted, and disubstituted amides. Among esters and carboxylic acids, an aromatic group conjugated to the carbonyl groups defeats the reaction. An aromatic ring elsewhere in the molecule does not interfere. The α,β-unsaturated acid crotonic acid appears to react only when a large excess of $NaBH_4$ is used and then gives the saturated alcohol, leading to the suspicion that the double bond is reduced first.

The reduction of L-phenylalanine to 2-amino-3-phenyl-1-propanol is noteworthy, although the yield was poor. The stereochemical outcome was not determined, but the reaction conditions would not be expected to racemize either the starting material or the product. The poor yield can be attributed, at least in part, to our difficulty in separating the product, which is fairly water soluble, from the reaction mixture.

Reduction of cyclohexene, by the procedure designed for acids and esters, gave a 10% yield of cyclohexane, identified by its NMR spectrum, in the methylene chloride extract. No starting material was found, and, judging by the spectroscopic results, most of it seemed to have been converted to a low molecular weight, hydrocarbon polymer.

Phenylacetonitrile was treated by the procedure designed for amides. Neither 2-phenylethylamine nor starting material could be found among the products.

These results are summarized in Tables I–III.

When diborane and Me_2SO are mixed in stoichiometric quantities at low temperature a solid, believed to be $[(CH_3)_2SO]_2BH_2^+BH_4^-$, is reported.[6] This material is re-

(6) Shone, S. G. *Inorg. Chem.* **1965**, *4*, 125–127.

ported to decompose explosively when allowed to warm to 0 °C.[6] Under the present, quite different, conditions no violent or explosive reactions were observed, although we have carried out over 100 reductions under these procedures.

An explosion has been reported when attempting to use dimethylformamide as a solvent for reductions with $NaBH_4$.[7] This was probably the result of the runaway reduction of the solvent.

Discussion

One can visualize two, fundamentally different, roles for the acid in these procedures. It can protonate the carbonyl group, activating it for attack by the hydridic reducing agent, or it can react with BH_4^-, liberating a solvated BH_3, which might then carry out the reduction. Most of the reductions reported here can, in fact, be carried out with tetrahydrofuran–borane;[8] however, the ease of reduction of various structural types is somewhat different. Aromatic as well as aliphatic acids are reduced, and esters are much more slowly reduced than acids.[8] With the present combination esters and acids are reduced with equal facility, and neither is reduced if there is an aromatic ring adjacent to the carbonyl group. Carbon–carbon double bonds are hydroborated by solvated BH_3.[9] Although the present conditions reduce crotonic acid to 1-butanol, cyclohexene is reduced only in very poor yield. Hydroboration in an acidic medium would be expected to give the reduction product, so this observation argues against the presence of BH_3. However, the dominance of an unknown competing reaction weakens the argument. Again, however, diborane disporportionates to $BH_2[OS(CH_3)_2]_2^+BH_4^-$ in the presence of Me_2SO under other conditions.[6]

Carbonyl oxygen protonation is a particularly attractive role for the acid in the case of the amide reductions, because amides are reasonably basic. Protonated amides have pK's between 0.0 and −2.0 in water,[10] and N,N-dimethylacetamide has a similar pK in Me_2SO.[11] These values indicate that there is a respectable concentration of protonated amide present in these reaction mixtures. Since the essential step in the reduction is a nucleophilic reaction at the carbonyl carbon, it is certain that reduction must be greatly facilitated by protonation, just as amide hydrolysis is so facilitated.[12] Reduction of protonated amide would be consistent with observed reductions in acidic solvents,[13] and in the presence of $POCl_3$ and Lewis acids.[13-15] It would also be somewhat analogous to the acid-induced reduction of alcohols, via the corresponding carbocations, by BH_3CN^- in the presence of acid.[16] The situation is less clear for esters and carboxylic acids, as these compounds are much less basic; their conjugate acids have pK values between −6 and −8[17] in water so there would be only very small concentrations of the conjugate acids in the presence reaction mixtures.

The main synthetic procedure with which the present methodology should be compared is reduction with lithium tetrahydridoaluminate (LAH).[18-21] By comparison with the present procedures, the LAH procedure offers somewhat better yields and, usually, easier product isolation. Also, a smaller molar excess of LAH is required.[19-21] The advantages of the present procedure are that the solvent need not be anhydrous, and Me_2SO is a far easier solvent to store and handle than the ethers which are used in the LAH reductions. Also, $NaBH_4$ is a far safer reagent than LAH. The present procedures also may offer somewhat different selectivity than LAH procedures.[8] The latter, for example, often attack carbon–halogen bonds, which are undisturbed by $NaBH_4$. Tetrahydrofuran–borane will generally accomplish the reductions described here,[8] and the isolation in that procedure appears more straightforward, but the reagent is extremely hazardous. For amides, the present method is similar in concept and outcome to the reduction of amides by $NaBH_4$ in dioxane as a solvent, in the presence of acetic or trifluoroacetic acid, described by Umino and co-workers.[22] The Umino method appears not to extend to esters and acids, however, and dioxane is now regarded as carcinogenic. We also believe that the present method of product isolation is generally superior.

Registry No. Hexanamide, 628-02-4; acetanilide, 103-84-4; N,N-dimethylbenzamide, 611-74-5; phenylacetic acid, 103-82-2; 4,4′-bis(dimethylamino)benzophenone, 90-94-8; hexylamine, 111-26-2; N-ethylaniline, 103-69-5; N,N-dimethylbenzylamine, 103-83-3; phenethyl alcohol, 60-12-8; 4,4′-bis(dimethylamino)diphenylmethane, 101-61-1; N-methyl-2-phenylacetamide, 6830-82-6; ε-caprolactam, 105-60-2; acetic acid, 64-19-7; d-phenylalanine, 673-06-3; crotonic acid, 3724-65-0; triacetin, 102-76-1; cyclohexene, 110-83-8; N-methylphenethylamine, 589-08-2; hexahydro-1H-azepine, 111-49-9; ethanol, 64-17-5; 2-amino-3-phenyl-1-propanol, 16088-07-6; butanol, 71-36-3; 1,2,3-propanetriol, 56-81-5; cyclohexane, 110-82-7; BH_4^-, 16971-29-2; Me_2SO, 67-68-5.

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