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Sodium Acyloxyborohydride as New Reducing Agents. I. Reduction of Carboxamides to the corresponding Amines

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A number of methods from carboxamides to the corresponding amines have been reported: lithium aluminium hydride, diborane[1a], lithium trimethoxyaluminium hydride[1b], aluminium hydride[1c], sodium borohydride-pyridine[1d], sodium borohydride-aluminium chloride[1e], lithium cyanoborohydride[1f], sodium borohydride-triethyloxonium fluoroborate[1g], etc[1h-i].

In 1960, Brown and Rao[2] suggested that in diglyme sodium borohydride and propionic acid most probably react as follows:

$$CH_3CH_2COOH+NaBH_4 \longrightarrow CH_3CH_2COOBH_3Na+H_2$$

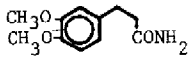
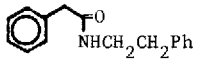
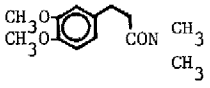
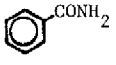
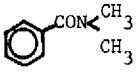
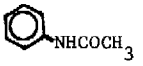
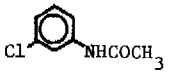
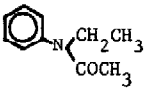
Afterwards, Marshall and Johnson[3] have reported the hydroboration of 1-hexene with sodium borohydride and acetic acid in tetrahydrofuran. However, little attention[4] has been paid to the reducing ability of such sodium acyloxyborohydride. Recently Gribble et al.[5] reported on the alkylation of amines with sodium borohydride in neat carboxylic acid, but N-acetyl indoline was recovered in 67% yield with sodium borohydride in neat acetic acid.

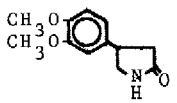
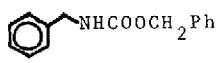
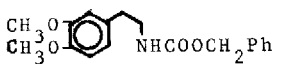
Now, we present a new convenient procedure for reduction of carboxamides to the corresponding amines, which is operationally simple, highly selective and efficient. Thus primary and secondary amides were found to be reduced quite easily by sodium acyloxyborohydrides prepared from an equivalent mole sodium borohydride and carboxylic acids in tetrahydrofuran or dioxane, while tertiary-amides gave only poor results. For the latter, however, trifluoroacetic acid was proved to be a satisfactory substitute of acetic acid; e.g. N-acetylindoline was converted to N-ethylindoline with sodium trifluoroacetoxy-

borohydride in 64% yield in refluxing dioxane for 5 hours, but only 28% yield with sodium acetoxyborohydride. Carbamates were also smoothly reduced to the corresponding amines. The results are summarized in Table I.

Table I

Reduction of Carboxyamides and Carbamates with Sodium Acyloxyborohydrides

Carboxamide	Solvent	Ratio Reagent/Amide	Time, hr	Yield of amine HCl%
	dioxane	5	4.5	71
	THF	10	2	92.5
	THF	10[a]	3	85.8[a]
	THF	10	3	82
	dioxane	5	20	27
	dioxane	5	4	76.2
	dioxane	5	2	82.5
	dioxane	10	17	35.1
	dioxane	10[b]	4.5	42.7[b]
	dioxane	5	1	88.1
	dioxane	5	1.5	89.5
	diglyme	5	1	83.8
	dioxane	5	20	20.1

Carboxamide	Solvent	Ratio Reagent/Amide	Time,hr	Yield of amine HCl%
	dioxane	10	5.5	60
	dioxane	10	5	28
	dioxane	10[b]	5	64[b]
	dioxane	4	5	65.7
	dioxane	5	2	82

a PhCOOH was used as carboxylic acid.
b CF_3COOH was used as carboxylic acid.

The following procedure for the reduction of benzamide is representative. To a stirred suspension of sodium borohydride (1.89g, 50mmole) and benzamide (1.21g, 10mmole) in dioxane (20ml) was added acetic acid (3.0g, 50mmole) in dioxane (10ml) over a period of 10 minutes at 10° and the resulting mixture was stirred under reflux for 2 hours. The reaction mixture was concentrated to dryness in vacuo, excess reagent was decomposed with water and extracted with chloroform. The extract was washed with water and dried over anhydrous sodium sulfate. The chloroform layer was treated with dry hydrogen chloride, evaporated in vacuo and the residue was crystallized from methanol-ether to give benzylamine hydrochloride (1.09g, 76.2%).

We believe that main reactive species in these reactions are not free diborane by reasons which follow. (1) Tertiary amides are not appreciably reduced with sodium borohydride and acetic acid. (2) The externally generated gases in the reaction of sodium borohydride and carboxylic acid (AcOH or CF_3COOH) in diglyme at 120° do not reduce N-(4-methoxyphenethyl)-3-(3-methoxyphenyl) propionamide in tetrahydrofuran nor do they make pyridine borate in tetrahydrofuran. (3) The analogously generated gases from the isolated powders[6] which can reduce various amides to the corresponding amines in high yield, do not reduce

N-(4-methoxyphenethyl)-3-(3-methoxyphenyl) propionamide.

Further applications of these versatile reagents are currently explored in our laboratory, and the results will be published in due course.

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