General Applicability of Pyridine:Borane and Morpholine:Borane as Reducing Agents.

INTRODUCTION

The reduction of carbonyl groups by various hydride reagents has been extensively investigated.[1] Most of the hydrides investigated were highly reactive, non-selective and difficult to work with on scale.[1] This paper describes efforts to evaluate the reducing capabilities of amine borane complexes which are much more robust and amiable on scale.

The most used source of borane is a commercially available tetrahydrofuran (THF) solution of borane:THF complex. This however is only available at low concentrations, is moisture sensitive and is prone to decomposition by ether cleavage of the THF ring leading to butoxyboranes. Lower temperatures and added stabilizers help to prevent this decomposition especially on storage.[1] Amine borane complexes generally are not moisture sensitive, are stable for up to 6 months at room temperature and are very useful for reductions and reductive aminations in protic media.

PROPERTIES

Pyridine borane was first prepared by Schlesinger and co-workers,[1] by the reaction of diborane and pyridine using vacuum techniques. It is a light yellow odorless liquid which is stable in air, insoluble in and only slightly hydrolyzed by water. It is very soluble in common organic solvents, but does tend to polymerize in higher boiling solvents.[1] Taylor and associates[1] developed a more convenient synthesis using anhydrous pyridine hydrochloride and sodium borohydride with pyridine as solvent. Additionally, it can be prepared by treating THF borane complex with pyridine.[1]

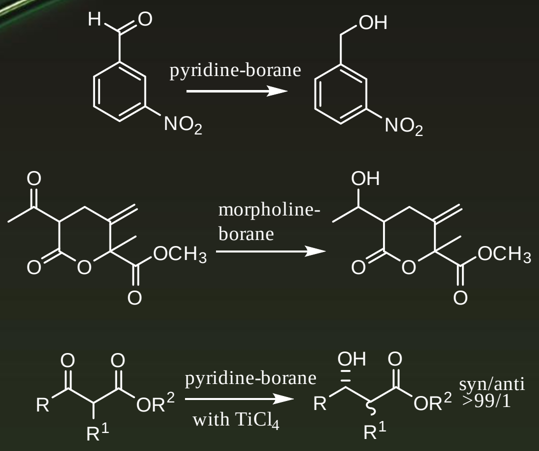
Morpholine borane was prepared and studied by Murray.[1] It is a white crystalline solid that is stable in air and very slowly hydrolyzed by water. This kinetic stability makes it a quite useful hydridic reagent in water and mixed aqueous solvents.[1] A comparison of selected hydride reagent properties is highlighted in Table 1.

Name	CAS #	Formula	m.p. (°C)	b.p. (°C)	d (g/mL)	comments
Sodium borohydride	16940-66-2	$NaBH_4$	>300	n/a	1.074	highly moisture sensitive
Sodium acetoxyborohydride	63947-71-7	$NaBH_3OAc$		n/a		highly moisture sensitive
Sodium triacetoxyborohydride	56553-60-7	$NaBHOAc_3$	118	n/a		moisture sensitive
Sodium cyanoborohydride	25895-60-7	$NaBH_3CN$	>242	n/a		highly moisture sensitive & toxic
Lithium aluminum hydride	16853-85-3	$LiAlH_4$	125	n/a	0.92	highly moisture sensitive & toxic
Diborane	19287-45-7	B_2H_6	n/a	-92	0.33	pyrophoric & toxic gas
Borane:THF complex	14044-65-6	BH_3:THF	n/a	n/a	0.88	Highly moisture sensitive
Pyridine:borane complex	110-51-0	Pyr:BH_3	11	decomp.	0.92	stable in air
Morpholine:borane complex	4856-95-5	Morph:BH_3	98	n/a		stable in air

Table 1: Properties of selected hydride reagents.

APPLICATIONS

Amine borane complexes have a wide range of physical and chemical properties that have been utilized in a variety of applications including polymers, dyes, metal plating[1] and pharmaceuticals.[1] Most amine boranes are used for their reducing capabilities as the strong complexation between boron and the amine limit their use in hydroboration reactions.[1] The reactivity of amine boranes can be manipulated through steric and electronic effects to selectively reduce certain functional groups in the presence of others (scheme 1)[1], or to facilitate the hydroboration of alkenes and alkynes.[1]



Scheme 1: Examples of selective reduction with amine-boranes.

The literature has numerous examples of amine boranes being used to reduce aldehydes[1], ketones[1], lactones, epoxides[1], esters[1], carboxylic acids, acid chlorides, amides[1], oximes[1], imines[1] and nitriles. Depending on the substrate involved, some of these reductions can be stereoselective[1] and/or result in reductive amination.[1]

RESULTS

The pyridine:borane and morpholine:borane complexes were both prepared in high yield with purities >95%. These two amine boranes were then evaluated for their ability to reduce substrates containing the various functional groups mentioned earlier (see Table 2 & 3). The initial reactions were all run at room temperature in THF and an equivalent of HCl (relative to amine borane) was added to facilitate the reaction. Any reaction that failed to proceed at room temperature (not listed in table) was further evaluated at higher temperatures. Some reaction times may not represent the actual time required for complete reduction as some experiments were allowed to stir over a weekend for convenience.

Table 2: Reductions with pyridine:borane complex.

Entry	Starting Material	Rxn Time (hrs.)	Rxn Temp. (^{o}C)	Product	Yield* (%)
1	Cyclohexanone	24	25	Cyclohexanol	81.5**
2	Benzamide	120	55	Benzylamine	0
3	Benzaldehyde	48	25	Benzyl alcohol	95
4	3-Bromobenzoic acid	90	55	3-Bromobenzyl alcohol	<10
5	4-Bromobenzonitrile	48	55	4-Bromo benzylamine	0
6	Benzoyl chloride	72	25	Benzyl alcohol	>90***
7	Valerolactam	84	25	Piperidine	0
8	Methyl 4-hydroxy benzoate	105	25	4-Hydroxybenzyl alcohol	0
9	Cyclohexanone oxime	24	25	N-hydroxy cyclohexylamine	>95
10	α-Methylstyrene	48	55	Isopropylbenzene	0
11	Nitrobenzene	72	55	Aniline	0
12	Styrene oxide	80	25	Phenethyl alcohol	>99
13	N-t-butylbenzylimine	30	25	N-t-butyl benzylamine	>95

* GC Yield unless otherwise stated

** Isolated Yield

*** Hydrolysis products also observed.

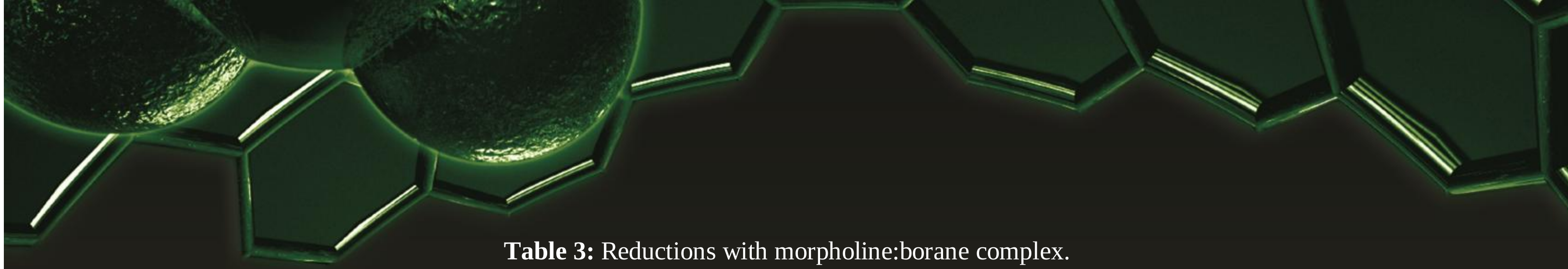


Table 3: Reductions with morpholine:borane complex.

Entry	Starting Material	Rxn Time (hrs.)	Rxn Temp. (^oC)	Product	Yield* (%)
1	Cyclohexanone	24	25	Cyclohexanol	95***
2	Benzamide	72	55	Benzylamine	0
3	Benzaldehyde	24	25	Benzyl alcohol	99***
4	3-Bromobenzoic acid	24	55	3-Bromobenzyl alcohol	0
5	4-Bromobenzonitrile	120	55	4-Bromo benzylamine	0
6	Benzoyl chloride	30	25	Benzyl alcohol	>90***
7	Valerolactam	60	55	Piperidine	0
8	Methyl 4-hydroxy benzoate	60	55	4-Hydroxybenzyl alcohol	0
9	Cyclohexanone oxime	72	25	N-hydroxy cyclohexylamine	>90***
10	alpha-Methylstyrene	48	55	Isopropylbenzene	0
11	Nitrobenzene	44	55	Aniline	0
12	Styrene oxide	48	55	Phenethyl alcohol	>99
13	N-t-butylbenzylimine	24	25	N-t-butyl benzylamine	>90***
* GC Yield unless otherwise stated					
** Isolated Yield					
*** Hydrolysis and reductive amination products also observed.					

SUMMARY

Amine boranes, such as pyridine:borane and morpholine:borane, are useful reducing agents. Unlike the metal hydride reagents, their stability to air and moisture and their solubility in a wide variety of organic solvents, make them ideal candidates for large scale use.[1] They are not as reactive as the metal hydrides which can limit their reducing ability, but this also offers the advantage of reducing certain functional groups in the presence of others. We have demonstrated the convenient preparation of these amine boranes and their ease of use in reducing specific functional groups. Table 4 below compares the reducing capabilities of various selected reducing agents.

	$NaBH_4$	$NaBH_3CN$	$NaBH_3OAc$	$NaBHOAc_3$	$LiAlH_4$	BH_3:THF	Pyr:BH_3	Morph:BH_3
Aldehydes	+	+	+	+	+	+	+	+
Ketones	+	+	+	+	+	+	+	+
Carboxylic acids	~	-	-	-	~	+	-	-
Esters	+	-	-	-	+	~	-	-
Acid chlorides	+	+	+	+	+	+	+	+
Amides	+	-	~	-	+	~	-	-
Epoxides	+	+	+	+	+	+	+	+
Lactones	+	-	-	-	+	+	-	-
Oximes	+	+	+	+	+	+	+	+
Imines	+	+	+	+	+	+	+	+
Lactams	+	-	-	-	+	+	-	-
Nitriles	+	-	-	-	~	+	-	-
Nitro	~	-	-	-	~	-	-	-
+ = reduction	- = no to minimal reduction		~ = partial to good reduction depending on conditions					

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