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Efficient reductions of dimethylhydrazones using preformed primary amine boranes

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ABSTRACT

A convenient method for the reduction of N,N-dimethylhydrazones using amine borane complexes generated *in situ* is described. It was found that primary amine borane complexes performed exceedingly well at reducing N,N-dimethylhydrazones in as little as 1.1 equivalents, furnishing the corresponding air-sensitive hydrazine products in excellent yields.

GRAPHICAL ABSTRACT



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KEYWORDS

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Introduction

We have previously reported that N,N-dimethylhydrazinoalkenes are versatile intermediates for metalloamination/cyclization leading to direct electrophilic functionalization.^[1–3] We have found that the reduction of precursor N,N-dimethylhydrazones using previously existing procedures is surprisingly tedious due to the extreme sensitivity of the product N,N-dimethylhydrazines to air exposure. Here we describe an exceptionally practical method for these reductions using primary amine boranes generated *in situ*. The reduction of N,N-dimethylhydrazones to the corresponding hydrazines has most commonly been achieved by using LiAlH₄, NaBH₄, pyridine borane, and NaBH₃CN.^[4–6] NaBH₃CN and pyridine borane have been described as more selective toward the C=N π system than LiAlH₄ and NaBH₄.^[4] The use of NaBH₃CN suffers from both its toxicity and expense, whereas pyridine borane entails a relatively tedious work up. Alternatively, Casarini has described the use of dimethylamine borane with *p*-toluenesulfonic acid for the reduction of α,β unsaturated hydrazones to provide allyl hydrazines.^[7] In addition, Perdicchia utilized trimethylamine borane and HCl gas for

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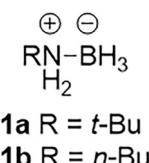


Figure 1. The general structure of the amine boranes used for the *in situ* reduction of N,N-dimethylhydrazones.

the reductions of hydrazones.^[8] More recent work has included the use of various tertiary amine boranes to reduce hydrazones and produce air stable hydrazine and hydrazide products. These methods, however, rely on the ability to trap the hydrazine product as a salt or to intercept it *in situ* with an electrophile.^[9,10]

Amine boranes are relatively expensive, but can be readily generated from the parent amine and either borane-dimethyl sulfide (BMS) or borane-THF.^[11-13] The objective of this study was to identify amine-boranes that could be prepared *in situ*, immediately prior to the reduction of dimethylhydrazones, to facilitate high yield reductions to dimethylhydrazines (Figure 1).

Results and discussion

The series of amines examined in this study comprised *n*-butylamine, *t*-butylamine, diethylamine, morpholine, dimethylethylamine, triethylamine, and pyridine. Aqueous solutions of alkylamines were not considered due to the rapid hydrolysis of BMS in the presence of water. The reduction efficiencies of the corresponding amine boranes (prepared *in situ*) were initially gauged with respect to their acid mediated reactions [using 1:5 (37%) HCl:MeOH (*v/v*)] with the N,N-dimethylhydrazone derived from 2-heptanone to provide dimethylhydrazine **2a** in the presence of methyl orange. It should be emphasized that cautious titrative addition of the acid was necessary to minimize premature hydrazone hydrolysis (Figure 2).

It was readily determined that both *t*-butylamine borane (**1a**) and *n*-butylamine borane (**1b**) were superior hydride sources to effect the desired reduction. Efficient reductions could be achieved with as little as 1.1 equiv. of **1a** or **1b** for the N,N-dimethylhydrazones of both 2-heptanone and 4-methylacetophenone (Table 1). Importantly, the reactant mixtures are air-sensitive *after basification*, and are facilitated by using Schlenk techniques. Borane adducts derived from the secondary amines diethylamine and morpholine were found to be inferior in that the reductions proved slower and the product N,N-dimethylhydrazine was contaminated with 2-heptanol, resulting from premature hydrazine hydrolysis. The boranes derived from tertiary amines (e.g., Me₂NEt and Et₃N) were even less effective. Although pyridine borane was a competent reductant, the subsequent removal of the pyridine byproduct was more tedious than the aforementioned primary amines.

Amine borane complexes **1a** and **1b** were then tested for their capability to reduce hydrazines derived from aldehydes (**3a**, **3b**, and **3c**). Initial tests using 1.1 eq of amine borane resulted in incomplete reduction of the starting hydrazones. However, 1.5 eq of

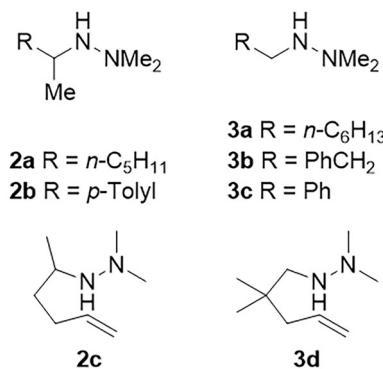


Figure 2. Structures of the N,N-dimethylhydrazine products prepared by the *in situ* reduction of the corresponding N,N-dimethylhydrazones by amine borane complexes.

Table 1. Preparation of hydrazines **2a**, **2b** and **2c** by reduction of the corresponding hydrazones using amine boranes **1a** and **1b**.

Hydrazine	Amine borane ^a	Equivalents	Yield (%)
2a	1a	3	88
2a	1a	1.5	86
2a	1a	1.1	83
2a	1b	3	86
2a	1b	1.5	80
2a	1b	1.1	84
2b	1a	3	87
2b	1a	1.5	86
2b	1a	1.1	90
2b	1b	3	90
2b	1b	1.5	92
2b	1b	1.1	94
2c	1a	1.5	71

^aPreformed from the corresponding amine and BMS *in situ*.

Table 2. Synthesis of hydrazines **3a**, **3b**, **3c**, and **3d** by the reduction of the corresponding hydrazones with amine borane complexes **1a** and **1b**.

Hydrazine	Amine borane ^a	Yield (%)
3a	1a	80
3a	1b	80
3b	1a	87
3b	1b	87
3c	1a	94
3c	1b	94
3d	1a	83

^aAll reactions performed with 1.5 eq of reactive amine borane complex.

amine borane complex proved to be adequate for the reduction of all three aldehyde-derived hydrazones in good yield (Table 2).

Amine borane complex **1a** was then tested for its capability to reduce the N,N-dimethylhydrazone precursors of some examples of our previously described N,N-dimethylhydrazinoalkenes.^[1-3] Using 1.5 eq of amine borane complex **1a** furnished N,N-dimethylhydrazinoalkenes **2c** and **3d** in good yield. It is especially noteworthy that these hydrazines were produced in high purity with no hydrazone precursor remaining, which was a major shortcoming of other previously existing procedures.

Conclusion

In conclusion, *t*-butylamine borane and *n*-butylamine borane, generated *in situ*, are unusually effective reducing reagents at moderately low pH. These provide a cost-effective, and simple method for the reduction of N,N-dimethylhydrazone to the corresponding hydrazines. The use of these reagents for the reduction of related C=N π systems will be described in the future.

Experimental

A representative procedure for N,N-dimethylhydrazone reduction is as follows: A 100 mL round-bottomed schlenk flask equipped with a magnetic stirring bar and an N₂ inlet was charged with *t*-butylamine (0.8 mL, 7.65 mmol) and dichloromethane (5 mL). The reactant mixture was cooled to 0 °C with stirring and BMS (0.75 mL, 10 M, 7.5 mmol) was added. The resulting solution was warmed to room temperature and stirred for 30 min. A solution of the appropriate N,N-dimethylhydrazone (5.00 mmol) and methyl orange (10 mg) in methanol (20 mL) was then added. The stirred reactant mixture was then cautiously titrated with a 1:5 HCl:MeOH (v/v) solution at room temperature until the solution maintained a pink/red color for 30 min. The volatiles were removed *in vacuo* leaving a pink/red residue. Aqueous sodium hydroxide (25% *w/w*) was added dropwise with stirring until a pH >10 was achieved. With the exclusion of air, diethyl ether (25 mL) was added to the resulting aqueous solution with vigorous stirring followed by the addition of pentane (10 mL). The resulting aqueous layer was separated and extracted with ether (10 mL), and the combined organic layers were dried with anhydrous sodium sulfate. The volatiles were removed *in vacuo* and the resulting oil was distilled from CaH₂ to afford the N,N-dimethylhydrazine as a clear to yellow liquid.

Full experimental details, ¹H NMR, ¹³C NMR, and HRMS data, where applicable, can be found in the “Supplementary Content” section of this article’s webpage.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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