



## Reductive amination with 5-ethyl-2-methylpyridine borane

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### ABSTRACT

We report a new amine borane, 5-ethyl-2-methylpyridine borane complex (PEMB) useful for reductive aminations of ketones and aldehydes in methanol or neat. Two of the three hydrides on PEMB are effectively utilized maximizing the economy of the reagent.

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### 1. Introduction

Amines are ubiquitous functionalities in current drugs and active pharmaceutical intermediates. Reductive amination of aldehydes and ketones is an important direct transformation of carbonyl compounds into amines.<sup>1</sup> In this important carbon–nitrogen bond forming process, aldehydes or ketones are reacted with ammonia, primary or secondary amines in the presence of a reducing agent to produce primary, secondary and tertiary amines, respectively. In the interest of efficient processes, the intermediate imine is not pre-formed. Therefore, the reducing agent used must be stable to conditions for the in situ formation of the imine or iminium ion since water is a co-product. In addition, the reduction of the ketone or aldehyde must be slower than imine formation and reduction to avoid alcohol by-products.

Besides formation of water in the condensation process, imines are generally formed under acidic catalysis, further limiting the types of reducing agents capable of withstanding aqueous acidic conditions. Acetic acid is commonly used for ketone amination due to favorable protonation of the hydroxyamine and loss of water. However, for aliphatic aldehyde reductions, acetic acid may increase the undesirable aldehyde reduction.

In order to successfully carry out a direct reductive amination, the choice of the reducing agent is very critical. Three acid stable reducing agents are sodium cyanoborohydride,<sup>2</sup> sodium triacetyloxyborohydrides,<sup>3</sup> and amine boranes.<sup>4</sup> Industrial use of sodium cyano-borohydride is unattractive due to toxicity and the large excess needed. Sodium triacetoxyborohydride, STAB, although quite selective for reductive amination, has only one hydride and is insoluble in most common organic solvents. In addition, STAB is often used in excess and cannot be utilized in protic solvents such as methanol, which favors imine formation. Catalytic hydrogenation has limited use with compounds containing double bonds, triple bonds; or hydrogen sensitive functionalities in the substrate.<sup>5</sup> Other reagents are non-selective in their reducing properties or

are decomposed in acidic media precluding an in situ direct reductive amination.

Amine boranes are effective reagents to carry out reductive aminations due to their acid stability and functional group compatibility.<sup>6</sup> Amine boranes derived from primary or secondary amines suffer from incorporation of the amine, therefore, are only appropriate for reduction of pre-formed imines. Amine boranes derived from tertiary amine or aromatic amines do not incorporate into the imine intermediate. In general, tertiary amine borane complexes are less reactive than aromatic amine borane complexes.

Although pyridine borane (PYB) has been demonstrated in successful reductive aminations, even at large scale,<sup>7</sup> it has a shelf-life of only 6 months and decomposes above 54 °C. Commercially available 2-picoline borane (PICB, mp 44–45 °C) has been demonstrated as a viable replacement for pyridine borane in reductive aminations.<sup>8</sup> Since liquid reagents can be easily contained and transferred from drums or cylinders via pipes, we have designed a liquid aromatic amine borane, 5-ethyl-2-methylpyridine borane (PEMB).<sup>9</sup> Thermal tests have demonstrated that the thermal stability of PEMB is greater than pyridine borane.

Because of the strong interaction of the nitrogen in pyridine compounds with Lewis acidic borane, 5-ethyl-2-methylpyridine borane (PEMB) is relatively stable toward hydrolysis (5% per day in water/THF) and methanolysis (6% per day). PEMB is highly soluble in tetrahydrofuran and toluene, up to at least 70 wt%, but it is essentially insoluble in aliphatic hydrocarbon solvents.

In summary, the advantageous properties of PEMB are the liquid physical state, the thermal stability at ambient temperatures, and the slow reaction with protic solvents. These characteristics of PEMB make it an attractive amine borane for selected reductions. The utility of PEMB in reductive aminations, Figure 1, is demonstrated in this Letter to promote this compound as a direct replacement for PYB.

### 2. Comparison of PEMB to PICB and PYB

To evaluate the potential of 5-ethyl-2-methylpyridine borane (PEMB) in organic synthesis, it was compared to pyridine borane

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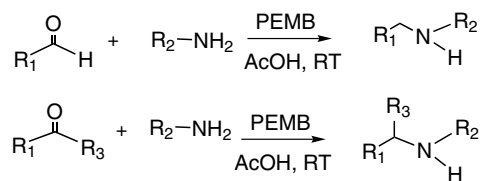


Figure 1. Reductive amination of aldehydes and ketones.

(PYB) and 2-picoline borane (PICB) in reductive amination of aldehydes and ketones in methanol. DiMare et al. observed that reductive aminations with pyridine borane were significantly faster in methanol than ethers or chlorinated hydrocarbon solvents. In addition, to support the 'green chemistry mindset',<sup>10</sup> reductions were conducted without solvent as a means to increase volume productivity and decrease solvent use. Previous reductive aminations with PYB or STAB were conducted at 0.25–0.5 M concentration, so a substantial increase in volume productivity can be achieved by conducting reactions without solvent.<sup>11</sup> The results of aldehyde and ketone amination are listed in Table 1. Comparative literature results for reductive amination with PICB<sup>8</sup> and PYB<sup>12</sup> are also listed.

In the comparative literature examples using PICB and PYB, a reagent ratio of 1:1:1 had been used for the carbonyl, amine, and amine borane reagents. To further increase the economic advantage of this process, the reagent ratio was aligned to use two of the three hydrides available in PEMB, thus a 2:2:1 ratio for the carbonyl, amine and PEMB was successfully used in all examples. In fact, in many reductions, 20–30% of the PEMB remained, which would allow for a higher ratio of substrate to PEMB.

Since carboxylic acid is beneficial for reductive amination, acetic acid (2 equiv of acetic acid relative to the carbonyl compound) was used in all reductions, except entry 4 with hexanal, which easily forms an imine. Most reactions were conducted at 20–25 °C by a slow addition of PEMB to the stirred mixture of amine and carbonyl substrate under nitrogen. Several of the less reactive ketones (entries 7, 8, and 9) were heated at 50 °C to increase reductive amination rate.

The reductive aminations with PEMB compare quite well with the results of these other aromatic amine borane complexes. The unoptimized yields were higher using PEMB than PYB in some examples, notably, the neat reductive amination of benzaldehyde with di-*n*-butylamine, entry 3, amination of hexanal without acetic

acid present, entry 4, and the reductive amination of 2-pentanone with weakly basic aniline, Entry 7.

PEMB was very selective toward reductive amination over carbonyl reduction. Competitive reduction of the ketone or aldehyde was not observed in any of the reactions except for entry 3 where benzaldehyde reduction to benzyl alcohol was the sole product in methanol. However, in the solvent-less reduction with PEMB, a high yield (96%) of desired tertiary amine was produced. Using PICB, Kikugawa et al. observed only a 48% yield of trialkylamine in 24 h while using an excess of di-*n*-propylamine without solvent and a 3% yield of amine and 77% benzyl alcohol with water as the solvent.

The aldehyde reductive aminations using PEMB occurred quite rapidly. For example, amination occurred in 2 h or less for benzaldehyde. For hexanal, the reductive amination without acetic acid was complete within 5 min after the PEMB addition. Similar fast reactions times have been observed with PICB and PYB in solvent. The cyclohexanone aminations were typically complete at ambient temperature within 1 h after the PEMB addition. For the reductive aminations without solvent, PEMB performed considerably faster than PICB. Kikugawa et al. reported reaction times of 3.5 and 15.5 h for entries 5 and 6, respectively. Presumably, the liquid state of PEMB gives it a strong kinetic advantage over solid PICB in solvent-less reductive aminations. Advantages of reductive amination with neat PEMB are rapid reactions and high reactor utilization as well as decreased amount of waste (solvent).

To demonstrate the scalability of using PEMB for reductive aminations without solvent, we conducted 0.2 mol reductive amination of hexanal with aniline. A 93% yield of *N*-hexylaniline was obtained after distillative removal of methyl borate and 5-ethyl-2-methylpyridine.

Because acyclic and aromatic ketones, especially acetophenone, only slowly undergo reductive amination, the reactions with 2-pentanone and acetophenone were heated at 50 °C to increase reaction rate. In contrast to PICB aminations of acetophenone with benzyl amine, which took 72 h at ambient temperature (both neat or in methanol), PEMB amination of acetophenone at 50 °C was complete in 4 h (neat), and 62% complete in 1 h in methanol.

The reductive amination process generates water as a co-product, therefore, the imine formation process could be inhibited in an aqueous system, especially for ketones and amines with high water solubility. In any event, reductive amination in water was demonstrated by Kikugawa et al. using PICB, obtaining slightly lower yields of amines from the aqueous system compared to reactions

Table 1  
Reductive amination of aldehydes and ketones; comparison of PEMB to 2-picoline borane and pyridine borane

Entry	Aldehyde or ketone/amine pairs	Yield <sup>a</sup> w/ PEMB in MeOH (%)	Yield <sup>a</sup> w/ PEMB neat (%)	Yield w/ PICB in MeOH (%)	Yield w/PICB neat (%)	Yield w/ PYB in MeOH (%)
1	Benzaldehyde/aniline	72	80	95	99	93 <sup>c</sup>
2	Benzaldehyde/benzylamine	87 <sup>b</sup>	92 <sup>b</sup>	76	NA	96
3	Benzaldehyde/ di- <i>n</i> -propylamine	0 <sup>d</sup>	96	NA	48 <sup>e</sup>	50 <sup>f</sup>
4	Hexanal/aniline w/o AcOH	92	94	82	77	91
5	Cyclohexanone/aniline	92	93	95	94	71, 93 <sup>c</sup>
6	Cyclohexanone/benzylamine	83 <sup>b</sup>	70 <sup>b</sup>	73	78	96
7	2-Pentanone/aniline	74	94	89	NA	27
8	2-Pentanone/benzylamine	84	83	79	63 <sup>g</sup>	80
9	Acetophenone/benzylamine	62 <sup>h</sup>	70	72	87	10, 69 <sup>c</sup>

<sup>a</sup> GC yield.

<sup>b</sup> Isolated as dialkylammonium acetate.

<sup>c</sup> Ref. 4a, reaction in petroleum ether with acetic acid.

<sup>d</sup> No reductive amination product, benzylalcohol generated.

<sup>e</sup> 24 h Reaction time with 3 equiv amine.

<sup>f</sup> Di-*n*-butylamine.

<sup>g</sup> Similar ketone.

<sup>h</sup> Percent conversion in 1 h.

**Table 2**  
Reductive amination of aldehydes and ketones; comparison of PEMB to sodium triacetoxyborohydride

Entry	Aldehyde or ketone/amine pairs	Yield <sup>a</sup> with PEMB in MeOH (%)	Yield <sup>a</sup> with PEMB neat (%)	Yield with STAB <sup>13c</sup> (%)
10	Benzaldehyde/aniline	72	80	88–95
11	Benzaldehyde/benzylamine	87 <sup>b</sup>	92 <sup>b</sup>	NA
12	Benzaldehyde/ di- <i>n</i> -Propylamine	0 <sup>c</sup>	96	64 <sup>d</sup>
13	Hexanal/aniline w/o AcOH	92	94	NA
14	Cyclohexanone/aniline	92	93	71
15	Cyclohexanone/benzylamine	83 <sup>b</sup>	70 <sup>b</sup>	88
16	2-Pentanone/aniline	74	94	90
17	2-Pentanone/benzylamine	84	83	81 <sup>d</sup>
18	Acetophenone/benzylamine	62 <sup>e</sup>	70	55 <sup>f</sup>

<sup>a</sup> GC yield.

<sup>b</sup> Isolated as ammonium acetate.

<sup>c</sup> No reductive amination product, benzylalcohol generated.

<sup>d</sup> BASF result.

<sup>e</sup> Percent conversion in 1 h.

<sup>f</sup> 240 h Reaction time.

in methanol or neat. We conducted one reductive amination of benzaldehyde and benzylamine with PEMB in water with acetic acid. The isolated yield of the dibenzylammonium acetate salt was only 69%. The lower yield compared to the amination without solvent (entry 2) can be attributed to loss of product to the aqueous solvent. PEMB is immiscible in water causing the reaction mixture to consist of the substrates and amine borane in a concentrated hydrophobic organic layer above the aqueous layer. The aqueous layer may facilitate heat transfer during exothermic reactions of the neat organic components.

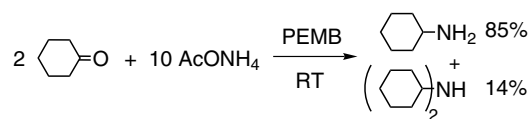
### 3. Comparison of PEMB to STAB

Sodium triacetoxyborohydride (STAB) has been demonstrated by Abdel-Magid et al. and others for reductive amination most often in 1,2-dichloromethane or THF. Typically, STAB is used in excess (from 1.4 to 4 equiv) and the carbonyl compound is the limiting reagent with a slight excess of amine (5–10%). STAB is a hygroscopic solid with low solubility in most solvents and cannot be used in alcohol or aqueous solvent. Table 2 lists the literature yields for reductive amination with STAB for comparison to our results using PEMB. Aldehyde aminations with STAB typically take 1–24 h at ambient temperature, while ketone amination with STAB typically requires at least 24 h at ambient temperatures, although for acetophenone the reaction required 10 days at ambient temperature. One limitation of STAB is that reaction mixtures should not be heated above 50 °C due to STAB self reduction and decomposition.

As stated above, reductive amination with PEMB was at ambient temperature for the aldehydes and cyclohexanone but at 50 °C for 2-pentanone and acetophenone. The results using PEMB are comparable to those reported for STAB and superior for entry 12 (reaction without solvent) and 14 as well as entry 17 and 18 where PEMB reductive amination at 50 °C is considerably faster than STAB.

For example, reduction amination of 2-pentanone with benzyl amine using STAB took 24 h at ambient temperature to reach 81% completion versus 2 h at 50 °C for the same reduction with PEMB (entry 17). Reductive amination of acetophenone with benzyl amine using PEMB also was quicker, 1 h at 50 °C in methanol and 4 h at 50 °C for the reaction without solvent as compared to STAB requiring 240 h at ambient temperature.

One largely unexplored area is the formation of primary amines from a ketone and ammonia or ammonium salt via amine borane induced reductive amination. Reductive amination with ammonium trifluoroacetate or ammonium acetate with STAB as the reducing agent in THF produced 80% dialkylated amine in 48 h.<sup>13</sup>



**Figure 2.** Reductive amination using ammonium acetate.

Ammonium acetate is insoluble in THF, 1,2-dichloroethane or acetonitrile, but soluble in methanol, so reductive amination using amine boranes may provide the desired primary amine. Using a 2:2:1 ratio of ketone, ammonium acetate and PEMB in methanol with acetic acid, we observed an instantaneous reduction. The products were a mixture of 49% cyclohexylamine and 50% dicyclohexylamine (relative product ratio). By use of an excess of ammonium acetate (Fig. 2, 5:1 relative to ketone) a higher yield of cyclohexylamine (85%) was produced, along with 14% dicyclohexylamine and 1% tricyclohexylamine.

An efficient, scalable, and high yielding method for reductive amination has been developed using, 5-ethyl-2-methylpyridine borane, PEMB. Two of the three hydrides on the borane are effectively utilized maximizing the economy of the reagent. This effective process to introduce an amino functionality into a molecule is rapid, and provides high reactor utilization when conducted without solvent. The benefits of solvent-less reductive amination with PEMB include cost savings due to decreased reactor time, decreased reactor size and capital investment, decreased energy consumption and high-pressure vessels are not necessary. PEMB is advantageous over solid PICB in the solvent-less reactions due to the liquid physical state of PEMB. The liquid physical state of PEMB also facilitates safe transfer from containers without physical exposure.

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### Supplementary data

Supplementary data associated with this article can be found, in the online version, at [doi:10.1016/j.tetlet.2008.06.095](https://doi.org/10.1016/j.tetlet.2008.06.095).

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9. Diborane (96 g, 3.4 mol) was added to neat 5-ethyl-2-methylpyridine (836.3 g, 6.90 mol) in a glass Parr vessel at ambient temperature. The temperature rose from 20 to 25 °C initially during the diborane addition then the chiller was set at 15 °C which kept the temp at 21.7 °C. The <sup>11</sup>B NMR spectrum of the solution showed a quartet at –13.2 (q, J = 98 Hz) 99.9% and 0.2% at –29 ppm (B<sub>3</sub>H<sub>8</sub><sup>–</sup>). Boron analysis: 99.8% of theory, Hydride: 100% of theory, Flashpoint: 221 °F/105 °C, Viscosity: 6.9 cs @ 20 °C, Density: 0.908 g/mL at 24 °C, 0.896 g/mL @ 55 °C Burkhardt, E.R. (BASF Corporation) U.S. Patent Application 60/846144, EP2007/060003.
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11. Benzylamine, 4.04 g (0.0377 mol), 4.00 g benzaldehyde (0.0377 mol) and 5 mL of glacial acetic acid were combined in a flask under N<sub>2</sub> and stirred for 15 min at room temperature before adding 2.67 g of PEMB (0.0198 mol) over 1 h via syringe. After the reaction was complete the reaction was refluxed with 50 mL of methanol and 1 mL of concentrated HCl to quench the excess borane followed by concentration at 50 °C and 152 mmHg to remove most of the methanol and methylborate. The white needle crystals are filtered, washed with chilled (0 °C) heptanes and dried for 2–3 h. Mp: 85.4 °C; <sup>1</sup>H NMR (300 MHz, d<sub>2</sub>-tetrachloroethane) δ 2.02 (3H, s), 3.90 (4H, s), 7.34 (10H, s), <sup>13</sup>C NMR (75.5 MHz, d<sub>2</sub>-tetrachloroethane) δ 22.47, 50.62, 128.68, 129.01, 129.61, 134.06, 176.97 ppm.
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