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Reductive amination agents: comparison of $Na(CN)BH_3$ and *Si*-CBH

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ABSTRACT

Reductive amination is a chemical reaction commonly employed by organic chemists in academics and the pharmaceutical industry. In this reaction a carbonyl group is converted to an amine via an imine intermediate, the formation of which is rate limiting. A major reagent necessary for the completion of this reaction is a hydride source, commonly sodium cyanoborohydride ($Na(CN)BH_3$). The objective of this research was to compare the efficacy of $Na(CN)BH_3$ with silica-bound cyanoborohydride (*Si*-CBH) as hydride sources in reductive amination reactions. Work has shown that reactions employing *Si*-CBH as a hydride source showed significant improvement, exhibiting an average percent conversion 25% greater than reactions using $Na(CN)BH_3$.

Reductive amination, also referred to as reductive alkylation, is one of the most important synthetic tools for the synthesis of amines. Some noteworthy examples of its use are the syntheses of delavirdine mesylate,[1] valsartan,[2] and amphetamine[3] (Fig. 1) to name a few. The typical reaction involves the coupling of an aldehyde or a ketone with an amine to initially yield a hydroxyamine, which subsequently forms an imine upon dehydration. This imine is then reduced to the substituted amine. The latter step can be performed in two different methods: either hydrogenation or reduction. Palladium, nickel, or platinum[4–6] catalyst can be employed in hydrogenation. Although this method is quite cost effective, there are limitations with additional functional groups that may be present; in particular, C=C, nitro, haloaromatic, etc.[7,8]

With reduction there tend to be less side products formed, however other issues are present. Various methods of performing this reaction have been developed, including solvent-free microwave reductive amination[9] and biochemical techniques such as protein immobilization.[10] Common agents used are borohydride based; some of which are $NaBH_4/Mg(ClO_4)_2$,[11] $Zn(BH_4)_2/ZnCl_2$,[12] $Na(OAc)_3BH$,[13–15] and $Na(CN)BH_3$,[16,17] the latter of which has shown the most use. Issues with this reagent are the toxicity of the sodium cyanoborohydride, as well as the side products that are formed during workup (HCN and NaCN).[18] Additionally, reactions employing $Na(CN)BH_3$ are usually performed with acetic acid, which can be problematic if acid labile groups are present. In an attempt to circumvent both the side product and acid sensitivity issues, we explored solid-support bound cyanoborohydride as an alternate source of hydride in reductive amination reactions. One such source is SiliaBond cyanoborohydride (*Si*-CBH) available from SiliCycle Inc. The cyanoborohydride is complexed to the quaternary ammonium modified silica gel surface at a loading of 1.0 mmol/gram. For our study we used a 1:2:2 ratio of carbonyl:amine:hydride.

Many combinations of carbonyls (0.1–0.25 g) and amines were tested (Table 1) in order to demonstrate the effectiveness of *Si*-CBH versus $Na(CN)BH_3$. We chose very benign reaction conditions, that is, room temperature, 24 h, in THF (10–25 mL). In order to obtain product for comparison with GCMS from a $Na(CN)BH_3$ reaction, the mixtures were quenched with distilled water (10–25 mL), extracted three times (10 mL) with ethyl acetate, washed with distilled water (10 mL), dried with $MgSO_4$, filtered, and evaporated. For reactions involving *Si*-CBH, however, the silica gel was simply filtered off and concentrated under reduced pressure. Conversions were obtained using GCMS.[19] Figure 2 illustrates typical spectra obtained. It can qualitatively be seen that the use of *Si*-CBH is superior to that of $Na(CN)BH_3$ in the reductive amination reaction of acetophenone with benzylamine.

Virtually every reaction performed had a higher product conversion percentage using *Si*-CBH (Table 1).[20] With benzylamine and benzaldehyde, an increase from 67.4% to 97.9% was observed when *Si*-CBH was used in place of $Na(CN)BH_3$. With benzylamine and 3-pentanone, the difference in yield between the two hydride sources used is even more pronounced. With $Na(CN)BH_3$ no product was observed after 24 h, and only 1.8% conversion after 48 h. In contrast, a conversion of 82.8% was observed after 24 h when using *Si*-CBH. There were some reactions, such as those involving *n*-hexylamine with benzaldehyde and heptaldehyde with benzylamine which exhibited similar conversion percentages (93.5 vs 99.8 and 95.5 vs 98.6%) when using $Na(CN)BH_3$ and *Si*-CBH, respectively. In addition, there were examples where no or very little product was formed with either reagent. Extremely low product conversions (commonly 0%) were noted for reactions

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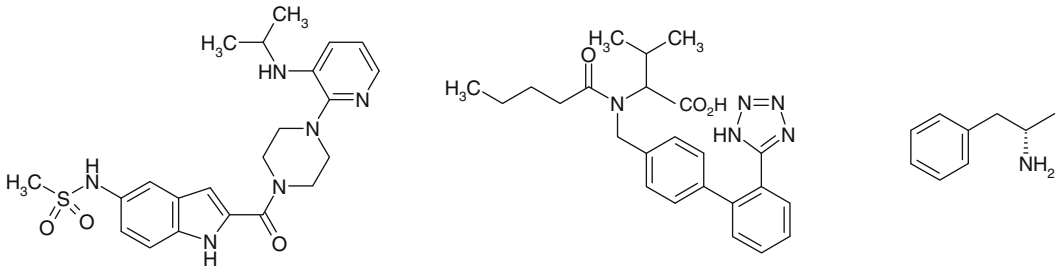
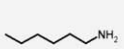
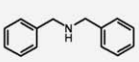
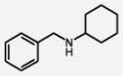
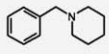
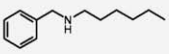
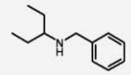
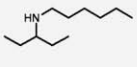
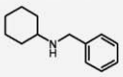
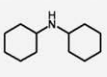
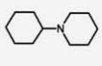
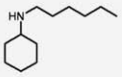
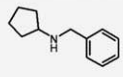
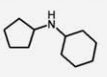
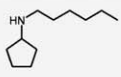
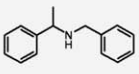
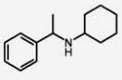
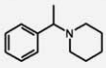
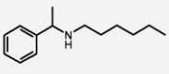
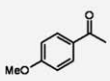
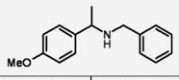
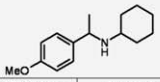
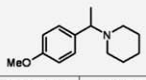
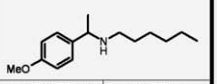
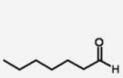
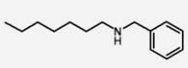
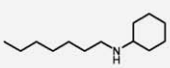
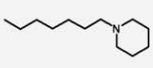
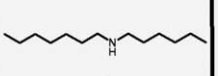


Figure 1. Shown left to right: delavirdine mesylate, valsartan, and amphetamine.

Table 1
Combinations of ketones/aldehydes (0.1–0.25 g) and amines used in reductive amination reactions (1:2:2 carbonyl:amine:hydride source) stirring at rt for 24 h in THF (10–25 mL)

Ketones/Aldehydes \ Amines				
	 NaCNBH$_3$: 67.4[49.1] / *Si*-CBH: 97.9[93.4]	 NaCNBH$_3$: 77.2 / *Si*-CBH: 99.6	 NaCNBH$_3$: 2.4(7.3) / *Si*-CBH: 69.3(82.9)	 NaCNBH$_3$: 93.5 / *Si*-CBH: 99.8
	 NaCNBH$_3$: 0.0(1.8) / *Si*-CBH: 82.8(89.5)	 NaCNBH$_3$: 0.0 / *Si*-CBH: 55.3	 NaCNBH$_3$: 0.0(0.1) / *Si*-CBH: 21.6(32.0)	 NaCNBH$_3$: 4.5[2.6] / *Si*-CBH: 79.4[68.7]
	 NaCNBH$_3$: 37.5 / *Si*-CBH: 93.3	 NaCNBH$_3$: 14.9[12.1] / *Si*-CBH: 97.5[80.5]	 NaCNBH$_3$: 1.6 / *Si*-CBH: 71.2	 NaCNBH$_3$: 66.5 / *Si*-CBH: 99.7
	 NaCNBH$_3$: 58.5 / *Si*-CBH: 99.2	 NaCNBH$_3$: 20.1 / *Si*-CBH: 96.3	 NaCNBH$_3$: 26.4[9.7] / *Si*-CBH: 95.5[94.2]	 NaCNBH$_3$: 63.2 / *Si*-CBH: 97.1
	 NaCNBH$_3$: 0.7 / *Si*-CBH: 27.5	 NaCNBH$_3$: 0.0 / *Si*-CBH: 2.4	 NaCNBH$_3$: 0.0(0.0) / *Si*-CBH: 0.0(0.0)	 NaCNBH$_3$: 1.4(2.3) / *Si*-CBH: 2.9(3.4)
	 NaCNBH$_3$: 0.3 / *Si*-CBH: 12.1	 NaCNBH$_3$: 0.0(0.0) / *Si*-CBH: 0.0(0.0)	 NaCNBH$_3$: 0.0(0.0) / *Si*-CBH: 0.0(0.0)	 NaCNBH$_3$: 1.4(1.7) / *Si*-CBH: 1.7(3.3)
	 NaCNBH$_3$: 95.5 / *Si*-CBH: 98.6	 NaCNBH$_3$: 42.7 / *Si*-CBH: 73.0	 NaCNBH$_3$: 68.3 / *Si*-CBH: 92.0	 NaCNBH$_3$: 51.8 / *Si*-CBH: 84.9

* ( ) indicates product percentages after 48 h.
* [ ] indicates isolated yield from 24 h reactions.

involving acetophenone or *p*-methoxyacetophenone. Most likely the initial nucleophilic attack of the amine onto the acetophenone is compromised by steric hindrance. Similarly, the poor yield with *p*-methoxyacetophenone can be attributed to steric as well as the electron-donating methoxy group decreasing the electrophilicity of the carbonyl carbon. Reactions between cyclohexylamine and 3-pentanone, as well as piperidine and 3-pentanone showed no product conversion using Na(CN)BH$_3$.

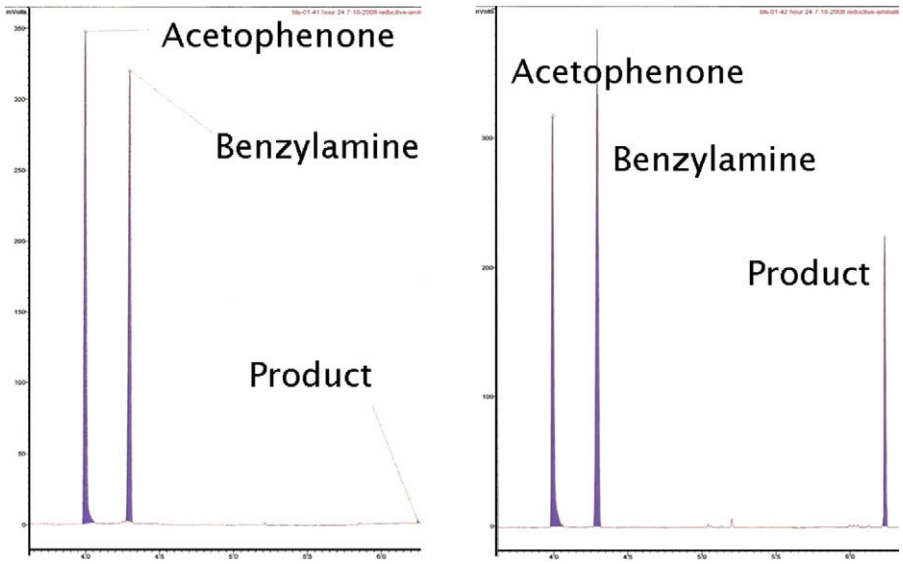


Figure 2. Gas chromatography spectra for reductive amination of acetophenone and benzylamine using $Na(CN)BH_3$ (left) or *Si*-CBH (right) as a hydride source.

The results depicted in Table 1 suggest that reductive amination reactions performed were markedly more effective when using *Si*-CBH as the hydride source. This suggests that the silica gel-based reagent is superior to the traditional reagent and is a choice better suited for reductive amination reactions in mild conditions.[21] The differences in *Si*-CBH that give the compound its remarkable improvement over the traditional hydride source are also of interest for future investigation. There are two possible properties that may explain the superiority of *Si*-CBH. Firstly, the structure of *Si*-CBH may provide pockets to facilitate intermolecular collisions. This could indicate that the silica gel is acting as a Lewis acid hence catalyzing the formation of the initial addition product. Alternatively, there may be residual H^+ ions on the silica gel, which would also catalyze the reaction.

Our results indicate that *Si*-CBH does perform much better in benign reductive amination conditions. In addition to providing superior conversions, acetic acid was not needed (eliminating issues with acid labile groups), the workup required only a filtration (decreasing amount of solvents used, as well as waste generated), and HCN and NaCN should not be liberated during workup. Although the cost of *Si*-CBH is higher than that of the traditional $Na(CN)BH_3$, its use may ultimately decrease overall expenditures by minimizing man-hours, as well as solvent waste generation.

Acknowledgments

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18. Moormann, A. E. *Synth. Commun.* **1993**, *23*, 789.
19. Varian CP-3800/Saturn 2200 GC/MS/MS: Injection volume: 5 μL; injection rate: 5 μL/s; injection temperature: 250 °C; column flow; 1.0 mL/min; column temperature: 40 °C, 5 min hold; 40–290 °C at 25 °C/min.
20. Products were confirmed either by comparison with authentic material or by using GCMS and/or NMR on purified product.
21. When acetic acid was added to the initial reaction both reactions were virtually quantitative.