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## Polymer-supported triacetoxyborohydride: a novel reagent of choice for reductive amination

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**Abstract**—A novel polymer-supported triacetoxyborohydride reagent for reductive amination of aldehydes and ketones is reported. The bound reagent was found to be shelf-stable and provided broad scope and reactivity in reductive amination reactions under mild reaction conditions. Streamlined protocols for its application in reductive amination reactions using both primary and secondary amines are described. © 2003 Elsevier Science Ltd. All rights reserved.

The use of polymer-supported reagents and scavengers<sup>1</sup> is a powerful tool for integrated organic synthesis and purification. By using bound reagents and scavengers the reaction by-products and excess starting materials can be selectively removed from the crude reaction mixture by simple filtration of resin. Immobilized reagents on polymer supports are particularly useful in high throughput parallel synthesis due to their well-known attributes for dispensing and removal from reaction mixtures. Moreover, polymer-supported reagents can provide unique advantages relative to their soluble counterparts including selectivity, isolable reactive intermediates and the ability to simultaneously use incompatible reagents, or perform multiple transformations in a single flask. In addition, they are adaptable to automated parallel synthesis and continuous flow reactors.<sup>2</sup>

Amines and their carboxamide derivatives comprise the most abundant structural moieties present in the comprehensive medicinal chemistry database.<sup>3</sup> The reductive amination of carbonyl compounds provides an expedient access to structurally diverse amines and has wide applications in synthetic organic chemistry.<sup>4,5</sup> The sequence proceeds through the formation of an imine or iminium intermediate upon reaction of a carbonyl compound with ammonia, primary amine or secondary amine followed by in situ reduction to an amine of higher order. A variety of borohydride-based reducing systems<sup>5</sup> have been developed for this transformation. Among these, sodium triacetoxyborohydride has

emerged as one of the most commonly employed reagents.<sup>6</sup> This reagent has gained preference relative to other reducing agents due to mild reaction conditions that are compatible with a variety of functional groups, and a broad scope of reactivity. However, sodium triacetoxyborohydride is moisture-sensitive and has poor solubility in most of the commonly used organic solvents. The reagent is therefore dispensed as a solid or slurry, thereby limiting its use in automated platforms. Following a reaction, product isolation requires an aqueous quench followed by liquid–liquid extraction and column chromatography further limiting the throughput in parallel synthesis.

In the context of our program on the development of polymer-supported reagents and scavengers for expedited organic synthesis, we envisioned a polymer-bound triacetoxyborohydride. Polymer-bound borohydride and cyanoborohydride reagents are known in the literature,<sup>7</sup> however, triacetoxyborohydride reagent on polymer support is unknown. Nonetheless, the scope and reactivity of bound borohydride and cyanoborohydride reagents in reductive amination reactions are limited in comparison to sodium triacetoxyborohydride. For example, bound cyanoborohydride requires moderately strong acidic reaction conditions<sup>7,8</sup> that are incompatible with acid-labile functional groups. The use of polymer-bound borohydride in reductive amination reactions is restricted as it lacks chemoselectivity. The reagent readily reduces carbonyl compounds along with imines and, therefore, is only suitable for reactions with preformed imines.<sup>9</sup> We describe here the first synthesis of an immobilized triacetoxyborohydride reagent<sup>10</sup> and demonstrate that it is a powerful reducing system for reductive amination reactions. The bound reagent

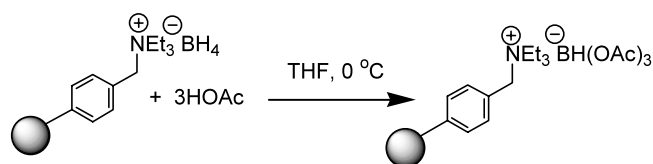
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offers broad scope and reactivity under mild reaction conditions, combined with the well-known attributes of a polymer-supported reagent for handling and purification.

Polymer-bound borohydride and cyanoborohydride resins have been prepared<sup>7</sup> by straightforward anion exchange reactions on quaternary ammonium chloride resins using aqueous solutions of the corresponding borohydrides. However, attempts to immobilize triacetoxymethylborohydride by anion exchange reaction on resin bound tetraalkylammonium chloride failed, as sodium triacetoxymethylborohydride is sparingly soluble in, or incompatible with, solvents used for ion exchange.

In an alternative approach, the polymer-bound triacetoxymethylborohydride reagent was conveniently synthesized in one-step from MP-Borohydride<sup>11</sup> (Scheme 1). Treatment of MP-Borohydride (capacity, 3 mmol/g) with 3 equiv. of glacial acetic acid in anhydrous THF afforded the supported triacetoxymethylborohydride in nearly quantitative yield, as revealed by the mass increase of the isolated resin. The active hydride content of the resulting resin was determined by measuring the volume of hydrogen gas evolved upon treatment of a resin sample with aqueous hydrochloric acid. The capacity was found to be 2.0 mmol/g or 99% of the theoretical value, indicating quantitative formation of the triacetoxymethylborohydride. The isolated resin typically contained about 10% (w/w) THF as calculated from the <sup>1</sup>H NMR spectrum of a CDCl<sub>3</sub> extract. In the process of synthesis and isolation of the triacetoxymethylborohydride resin, we discovered that the residual THF was critical to retain the activity of the resin. When all THF was removed by vacuum drying at the end of the synthesis, as normally done in resin isolation, the dried resins showed little or no activity within a few days. This is an unusual finding since a similar effect with sodium or tetraalkylammonium triacetoxymethylborohydride is unknown. The THF imbibed reducing polymer remained stable towards storage without any loss of activity and behaved like free-flowing dry beads in their handling rather than like a wet solid. This novel reducing system, further referred to as MP-Triacetoxymethylborohydride, proved to be a highly effective reagent for reductive amination reactions.

The scope and reactivity of MP-Triacetoxymethylborohydride have been evaluated for the synthesis of secondary and tertiary amines (Table 1). Typical conditions for reductive amination required 2.5 equiv. of MP-Triacetoxymethylborohydride relative to the limiting reagent. The reactions proceeded overnight at room temperature in tetrahydrofuran (THF) and unlike the case of sodium

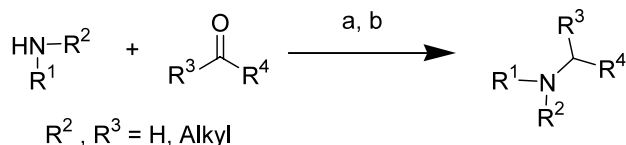


**Scheme 1.** Synthesis of MP-Triacetoxymethylborohydride.

triacetoxymethylborohydride, no acetic acid was required (Scheme 2). THF was found to be preferred to dichloroethane (DCE) due to the incompatibility of reactive amines with chlorinated solvents. Polar aprotic solvents, e.g. *N,N*-dimethylformamide (DMF) or *N*-methylpyrrolidinone (NMP), were effective solvents for substrates with low solubility in THF.

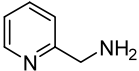
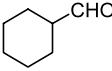
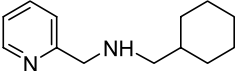
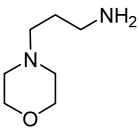
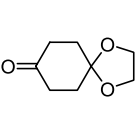
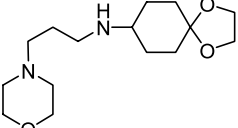
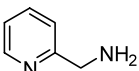
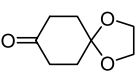
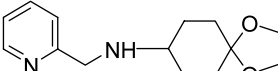
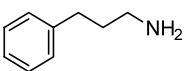
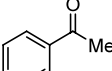
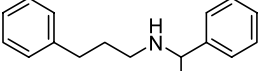
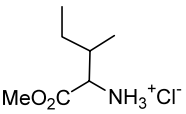
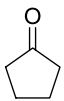
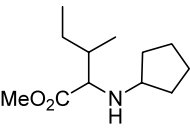
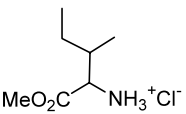
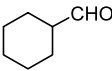
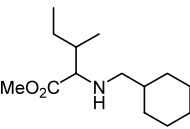
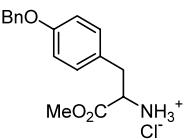
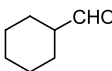
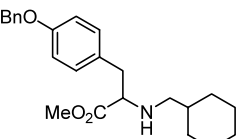
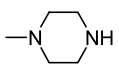
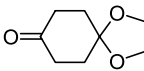
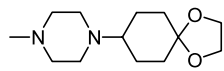

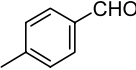
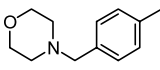
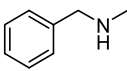

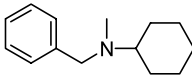
For synthesis of secondary amines, the starting primary amine was used in 20% excess in order to control selectivity toward monoalkylation. After the reaction was complete a bound aldehyde, PS-Benzaldehyde,<sup>12</sup> was added to the reaction mixture to selectively scavenge the excess primary amine. Products were then isolated in pure form by simple filtration and evaporation of solvent. The results are summarized in Table 1. The product amines were characterized by GC and NMR analysis.<sup>13</sup> Acid sensitive functional groups were tolerated, as exemplified by successful reductive amination of 1,4-cyclohexanedione mono-ethylene ketal (entries 2, 3 and 8, Table 1). Acetophenone underwent reductive amination consistent with sodium triacetoxymethylborohydride (entry 4, Table 1). Reductive amination using secondary amines was carried out with carbonyl compounds as the limiting reagent.<sup>14</sup> Upon completion of the reaction a bound isocyanate, PS-Isocyanate,<sup>12</sup> was added to the reaction mixture to selectively scavenge excess secondary amine. Cyclic and acyclic secondary amines were effective substrates (entries 8–10, Table 1). These reactions may also be carried out with the secondary amine as the limiting reagent to drive the reaction to completion. In these cases, the product amines were purified from non-basic impurities by 'catch and release' using a polymer-bound sulfonic acid, MP-TsOH.<sup>12</sup>

Reductive amination using hydrochloride salts of amino esters was carried out using DMF in the presence of 3.5 equiv. of MP-Triacetoxymethylborohydride with amine as the limiting reagent (entries 5–7, Table 1).<sup>15</sup> The additional equivalent of resin was used to neutralize the HCl present in the form of amine hydrochloride. Notably, overalkylation was not observed even in the presence of excess carbonyl compound. DMF and NMP were equally effective. Since carbonyl compounds were used in excess, the products were purified by 'catch and release' using MP-TsOH.<sup>12</sup> This method effected convenient DMF separation from the product by elution with MeOH prior to product release with ammonia/methanol.



**Scheme 2.** Reductive amination using primary and secondary amines. *Reagents:* (a) MP-BH(OAc)<sub>3</sub>, 2.5 equiv., THF; (b) PS-Benzaldehyde (R<sup>2</sup>=H) or PS-NCO (R<sup>2</sup>=alkyl) or MP-TsOH.

**Table 1.** Examples of reductive amination reactions using MP-Triacetoxyborohydride

Entry	Starting Amine	Carbonyls	Product Amine	%Yield	% Purity
1				90	96 <sup>a</sup>
2				77	100
3				91	100
4				39	91
5 <sup>b</sup>				59	98
6 <sup>b</sup>				93	99
7 <sup>b</sup>				74	98
8				85	100
9				63	100
10				82	100

<sup>a</sup> Dialkylated product (4 %) was present as the impurity. <sup>b</sup> DMF was used as the solvent.

In summary, we have described the first synthesis of polymer-bound triacetoxyborohydride. The novel reagent system was isolated with a high capacity of 2 mmol/g and found to be shelf-stable in the presence of residual THF. MP-Triacetoxyborohydride displayed

wide scope in reductive amination chemistry along with the benefits of integrated synthesis and purification associated with immobilized reagents. Further studies expanding the scope of this reagent are underway and will be reported shortly.

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11. MP-Borohydride, a macroporous triethylammonium methylpolystyrene borohydride, is commercially available from Argonaut Technologies.
12. The polymer-bound reagents PS-Benzaldehyde, PS-Isocyanate and MP-TsOH were obtained from Argonaut Technologies.
13. Reductive amination using primary amine (entry 2, Table 1): A THF solution of *N*-(3-aminopropyl)morpholine (1.2 mL, 0.6 mmol, 0.5 M) was added to a THF solution of 1,4-cyclohexanedione mono-ethylene ketal (1 mL, 0.5 mmol, 0.5 M). MP-Triacetoxymethylborohydride (2 mmol/g, 0.625 g, 1.25 mmol) was then added and the mixture was agitated for 16 h at room temperature. After which PS-Benzaldehyde<sup>12</sup> (0.42 g, 0.5 mmol) and THF (3 mL) were added and the mixture was further agitated for a period of 6 h. The solution was filtered and the resin was washed with THF. The combined solution was concentrated to afford the product secondary amine as the acetate salt in 77% yield and 100% purity, as characterized by gas chromatography and <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>).
14. Reductive amination using secondary amines (entry 8, Table 1): A THF solution of *N*-methylpiperazine (1.2 mL, 0.6 mmol, 0.5 M) was added to a THF solution of 1,4-cyclohexanedione mono-ethylene ketal (1 mL, 0.5 mmol, 0.5 M). MP-Triacetoxymethylborohydride (2 mmol/g, 0.625 g, 1.25 mmol) was then added and the mixture was agitated for 16 h at room temperature. After which PS-Isocyanate<sup>12</sup> (0.4 g, 0.5 mmol) and THF (2 mL) were added and the mixture was further agitated for a period of 6 h. The solution was filtered and the resin was washed with THF. The combined solution was concentrated to afford the tertiary amine product in 85% yield and 100% purity, as identified by <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>) and GC analysis.
15. Reductive amination of amine hydrochloride (entry 7, Table 1): A DMF solution of HCl-Tyr(OBn)-OMe (2 mL, 0.5 mmol, 0.25 M) was added to a DMF solution of cyclohexylcarboxaldehyde (1.2 mL, 0.6 mmol, 0.5 M). MP-Triacetoxymethylborohydride (2 mmol/g, 0.875 g, 1.75 mmol) was then added and the mixture was agitated for 16 h at room temperature. The resin was filtered and washed with DMF. The combined filtrate was agitated with MP-TsOH<sup>12</sup> (1 g, 1.5 mmol) for 45 min. The MP-TsOH resin was filtered and washed with MeOH (4×8 mL) to remove non-basic impurities. The amine product was released from MP-TsOH by washing with 2 M NH<sub>3</sub>/MeOH, and MeOH (2×8 mL). The combined solution was concentrated to afford the secondary amine product in 74% yield and 98% purity. The secondary amine was characterized by GC and <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>).