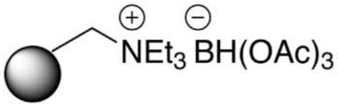
Technical Note 500

MP-Triacetoxyborohydride

Polymer-Bound Reducing Agent



Chemical Name: Macroporous triethylammonium methylpolystyrene triacetoxyborohydride

Resin Type: Macroporous polystyrene

Loading: 1.8–2.4 mmol/g (based on hydrogen evolution in 1 M HCl)

Bead Size: 350–1250 µm, 18–52 mesh (95% within)

Application: Reductive amination with primary and secondary amines

Typical Conditions for Reductive Amination: 1.0 mmol of carbonyl compound, 1.2 mmol of primary or secondary amine in THF, and 2.5 mmol of the resin stirred overnight at room temperature. For many of these reactions PS-Benzaldehyde or PS-Isocyanate may be added as scavengers for one-pot purification of the product.

Compatible Solvents: THF (2 mL/g), DMF (2 mL/g), N-methyl pyrrolidinone (NMP) (2 mL/g)

Composition: MP-Triacetoxyborohydride stabilized with 10% THF by weight

Storage: Should be stored in a closed container at 5 ˚C. However, the resin has been found to be stable at room temperature for at least several weeks. The resin contains 10% THF, which is required for stability. Removal *in vacuo* will lead to loss of activity.

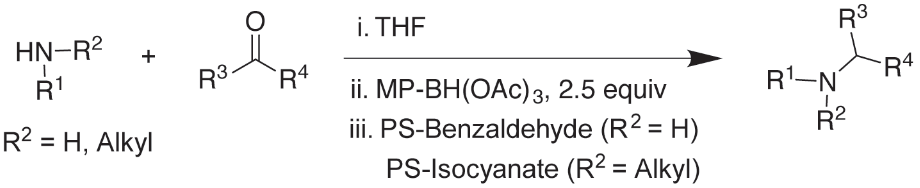
MP-Triacetoxyborohydride is a macroporous polystyrene-bound equivalent of tetraalkylammonium triacetoxyborohydride. MP-Triacetoxyborohydride has primary applications in the reductive amination of aldehydes and ketones under neutral or mildly acidic reaction conditions. This resin was developed to perform in a manner similar to that of the well-established sodium triacetoxyborohydride, while simplifying reagent handling and product purification. Moreover, for many of these reactions, a scavenger resin may be added for one-pot purification of the product. MP-Triacetoxyborohydride contains approximately 10% tetrahydrofuran (THF) and handles as free-flowing, low-static beads.

Sodium triacetoxyborohydride has emerged as one of the reagents used most frequently for carrying out reductive amination of carbonyl compounds, a reaction that is also known as reductive alkylation of amines.[1,2,3] This reagent has gained preference relative to other reducing agents as a result of its mild reaction conditions and broad scope of reactivity.
The typical conditions for reductive amination reactions with sodium triacetoxyborohydride utilize 1.5–2.0 equiv of reagent in THF or dichloroethane (DCE) in the presence of acetic acid. A disadvantage of sodium triacetoxyborohydride is its poor solubility, requiring reagent addition as a solid or slurry. Product isolation requires an aqueous quench followed by liquid-liquid extraction and column chromatography.

PART NUMBER	QUANTITY
800413	10 g
800414	25 g
800415	100 g
800416	1000 g

MP-Triacetoxyborohydride offers scope and reactivity similar to that of sodium triacetoxyborohydride with the additional convenience of a polymer-supported reagent for handling and purification. Typical conditions require 2.5 equiv of resin relative to the limiting reagent in THF. Acetic acid is not required (**Scheme 1**). After the reaction is complete, a scavenger resin may be added for product purification. For example, in the case of reductive alkylation using an excess of primary amine, PS-Benzaldehyde may be used to scavenge the excess starting primary amine from the product secondary amine. Likewise, in the case of reductive alkylation of secondary amines, an excess of the starting secondary amine may be scavenged by PS-Isocyanate. The product is then isolated by simply filtering the resins. "Catch and release" of the amines with MP-TsOH or SCX may also be employed to purify the reductive amination products when an excess of carbonyl compounds is used.[4]

Sodium triacetoxyborohydride is highly moisture-sensitive and sparingly soluble in common organic solvents, making it difficult to use in automated and parallel synthesis. The bound triacetoxyborohydride, on the other hand, may be used with resin dispensing systems. THF should be used as solvent in preference to DCE because of the incompatibility of reactive amines with DCE. This appears to be exacerbated by the presence of resin. Polar aprotic solvents, e.g. N,N-dimethylformamide (DMF) or N-methyl pyrrolidinone (NMP), may be used for substrates with low solubility in THF. These solvents allow use of amine hydrochlorides directly without prior conversion to the free amine. The scope and reactivity of MP-Triacetoxyborohydride for secondary and tertiary amine synthesis are described in more detail in the following sections.



Scheme 1: Reductive Alkylation of Primary and Secondary Amines

SYNTHESIS OF SECONDARY AMINES

The starting primary amine was used in 20% excess in order to control selectivity towards monoalkylation. Reductive amination reactions proceeded overnight at room temperature in THF under neutral reaction conditions. After the reaction was complete, PS-Benzaldehyde was added to the reaction mixture, selectively scavenging excess primary amine. The scavenging of primary amines proceeded to completion with no addition of acetic acid. Similar reactions using MP-Cyanoborohydride required 30% (vol.) acetic acid for complete scavenging of primary amines. We attributed the higher reactivity of the scavenger resin to the presence of excess MP-Triacetoxyborohydride, which acts as a dehydrating agent to drive imine formation with PS-Benzaldehyde. The product secondary amines were isolated as acetate salts by filtration of the resin and evaporation of the solvent. The free amine may be obtained by neutralization of the acetate salt with MP-Carbonate or by "catch and release" purification with MP-TsOH or SCX columns. We attributed the formation of the acetate salt to hydrolysis of an equivalent of triacetoxyborohydride by the water generated from imine formation prior to reduction.

The results for the reductive alkylation for a set of primary amines are summarized in **Table 1**. In most of the cases the products were isolated in excellent purity. Reaction of cyclohexanecarboxaldehyde afforded 16% and 4% overalkylated tertiary amine product with N-(3-aminopropyl)morpholine and 2-(aminomethyl)pyridine, respectively (**entries 1 and 2, Table 1**). Acid sensitive functional groups were tolerated, as exemplified by successful reductive amination of 1,4-cyclohexanedione mono-ethylene ketal with N-(3-aminopropyl)morpholine and 2-aminomethylpyridine (**entries 3 and 4, Table 1**). Acetophenone underwent reductive amination in low to moderate yields, which is consistent with results obtained with sodium triacetoxyborohydride (**entries 5 and 6, Table 1**).[1]

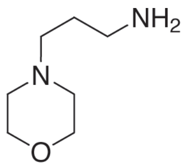
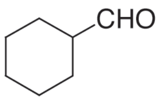
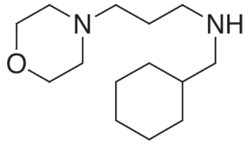
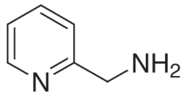
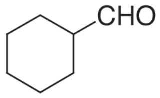
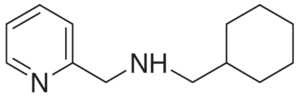
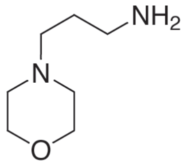
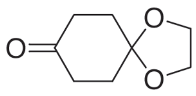
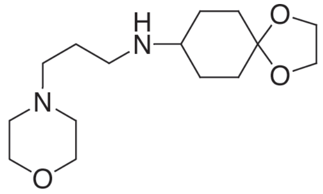
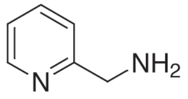
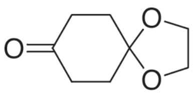
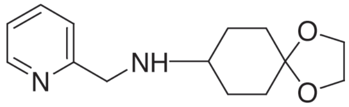
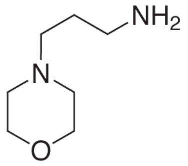
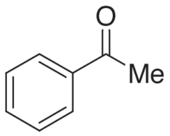
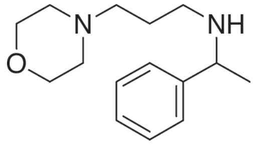
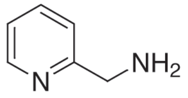
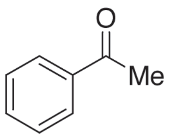
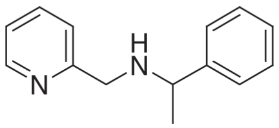
Reductive alkylation of hydrochloride salts of amino esters was carried out using DMF as the reaction solvent. Reactions were performed in the presence of 3.5 equiv of MP-Triacetoxyborohydride with amine as the limiting reagent. The additional equivalent of resin was used for amine hydrochloride neutralization. Results are shown in **Table 2**. Isoleucine methyl ester hydrochloride underwent reductive alkylation with cyclopentanone and cyclohexanecarboxaldehyde, respectively, to afford the corresponding secondary amine products in high yield and purity (**entries 1 and 2, Table 2**). Notably, overalkylation was not observed even though the carbonyl compound was in excess. Reductive alkylation of tyrosine methyl ester hydrochloride afforded analogous results (**entries 3 and 4, Table 2**). NMP was equally effective as the solvent for these reactions. Since carbonyl compounds were used in excess, the products were purified by "catch and release" using MP-TsOH. This method effected convenient DMF removal from the product, since the MP-TsOH-amine complex can be washed with methanol prior to product release in ammonia/methanol.

SYNTHESIS OF TERTIARY AMINES

Reductive alkylation of secondary amines was carried out with carbonyl compounds as the limiting reagent. Similar to the reactions with primary amines, these reactions proceeded overnight at room temperature in dry THF. Upon completion of the reaction, PS-Isocyanate was added to the reaction mixture to selectively scavenge excess secondary amine. Tertiary amine product was isolated as a free amine by filtration and subsequent evaporation of the solvent. Reductive amination using secondary amines may also be carried out with the amine as the limiting reagent to drive the reaction to completion. In these cases, the product amines may be purified from non-basic impurities by "catch and release" using MP-TsOH.

The results from the reductive alkylation of a set of secondary amines are summarized in **Table 3**. The expected products were obtained for both cyclic secondary amines with aldehydes and ketones (**entries 1 – 4, Table 3**). Alicyclic secondary amines, e.g. N-benzylmethylamine also underwent smooth transformation to the corresponding tertiary amines (**entries 5 and 6, Table 3**). In all cases the products were isolated in essentially pure form by simple concentration.

Table 1: Reductive Alkylation of Primary Amines using MP-Triacetoxyborohydride

Entry	Starting Amine	Carbonyl Compound	Product Amine	% Yield (isolated)	% Purity
1				77	84[a]
2				90	96[a]
3				77	100
4				91	100
5				69	98
6				76	27

a) Dialkylated product present as the major impurity.

Table 2: Reductive Alkylation of Amino Ester Hydrochlorides using MP-Triacetoxyborohydride in DMF

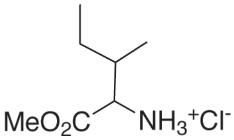
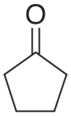
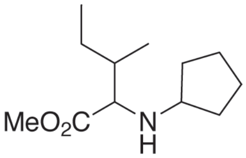
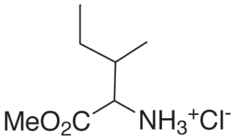
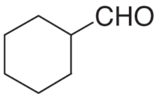
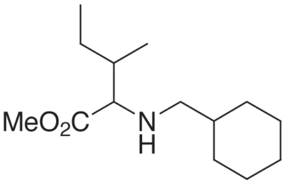
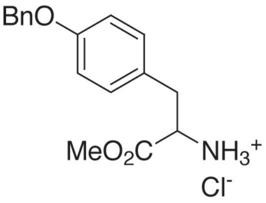
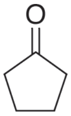
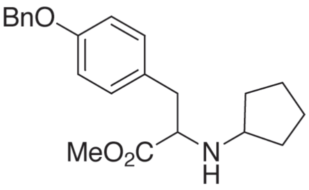
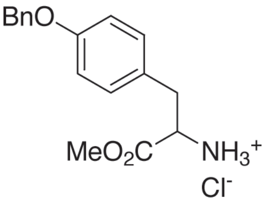
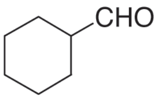
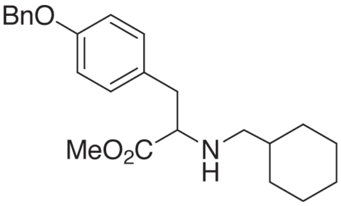
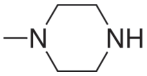
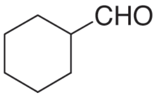
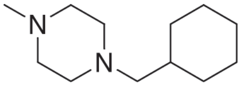
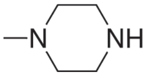
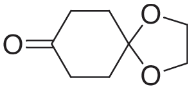
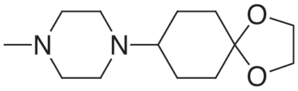
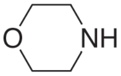
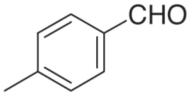
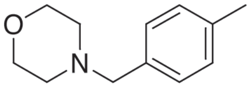
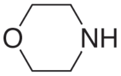
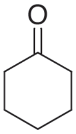
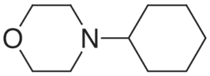
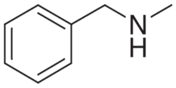
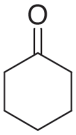
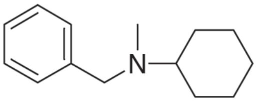
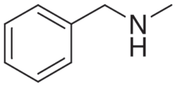
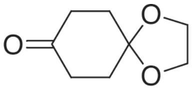
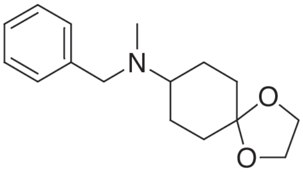
Entry	Starting Amine	Carbonyl Compound	Product Amine	% Yield (isolated)	% Purity
1				59	98
2				93	99
3				60	93
4				74	98

Table 3: Reductive Alkylation of Secondary Amines using MP-Triacetoxyborohydride

Entry	Starting Amine	Carbonyl Compound	Product Amine	% Yield (isolated)	% Purity
1				92	99
2				85	100
3				63	100
4				69	100
5				82	100
6				76	100

Boron Impurities

The reductive amination products were analyzed for the presence of boron by elemental analysis. The level of boron found was less than 100 ppm in all samples.

Capacity and stability

The triacetoxyborohydride content of the resin is determined by hydrolyzing the resin with aqueous HCl (1 M). The capacity is calculated based on the amount of liberated hydrogen gas collected. The resin typically contains approximately 10% THF (as calculated from the ^{1}H NMR spectrum of a $CDCl_3$ extraction of the resin). **The THF is required to stabilize the resin and it is important not to remove this by drying *in vacuo*.** The resin is stable for at least ten months at 4 °C in a closed container. Storage of samples for multiple weeks at room temperature does not affect the resin.

EXPERIMENTAL

Representative Procedure for Reductive Alkylation of Primary Amines (**Entry 3, Table 1**): A THF solution (0.50 M) of N-(3-aminopropyl)morpholine (1.2 mL, 0.60 mmol) was added to a THF solution (0.50 M) of 1,4-cyclohexanedione *mono*-ethylene ketal (1.0 mL, 0.50 mmol). MP-Triacetoxyborohydride (2.0 mmol/g, 0.625 g, 1.25 mmol) was then added and the mixture was agitated for 16 h at room temperature. When the reaction was complete, PS-Benzaldehyde (0.42 g, 0.5 mmol) and THF (2 mL) were added and the mixture was further agitated for 6 h. The solution was filtered and the resin was washed with THF (2 x 4 mL). The combined solution was concentrated to afford the product secondary amine as the acetate salt in 77% yield and 100% purity. The secondary amine was characterized by gas chromatography and ^{1}H NMR.

Representative Procedure for Reductive Alkylation of Primary Amine Hydrochlorides (**Entry 3, Table 2**): A DMF solution (0.25 M) of HCl-Tyr(OBn)-OMe (2 mL, 0.5 mmol) was added to a DMF solution (0.5 M) of cyclopentanone (1.2 mL, 0.60 mmol). MP-Triacetoxyborohydride (2.3 mmol/g, 0.760 g, 1.75 mmol) was then added and the mixture was agitated for 16 h at room temperature. The resin was filtered with a 6-mL fritted polypropylene cartridge into a scintillation vial containing MP-TsOH (1.0 g, 1.5 mmol). The MP-Triacetoxyborohydride resin was rinsed with DMF (3 x 2 mL) and the combined filtrate was agitated with MP-TsOH for 45 min. The mixture was transferred to a polypropylene cartridge fitted with a nylon stopcock to control the flow rate to approximately 0.5–1.5 mL/min. The MP-TsOH resin was washed with MeOH (4 x 8 mL) to remove non-basic impurities. The product was released by washing with 2 M NH_3/MeOH, and MeOH (2 x 8 mL). The combined solution was concentrated to afford the secondary amine product in 60% yield and 93% purity. The secondary amine was characterized by gas chromatography and ^{1}H NMR.

Representative Procedure for Reductive Alkylation of Secondary Amines (**Entry 1, Table 3**)*:* A THF solution (0.5 M) of N-methylpiperazine (1.2 mL, 0.60 mmol) was added to a THF solution (0.5 M) of cyclohexanecarboxaldehyde (1.0 mL, 0.50 mmol). MP-Triacetoxyborohydride (2.0 mmol/g, 0.625 g, 1.25 mmol) was then added and the mixture was agitated for 16 h at room temperature. When the reaction was complete, PS-Isocyanate (0.4 g, 0.5 mmol) and THF (2 mL) were added and the mixture was further agitated for 6 h. The solution was filtered and the resin was washed with THF (4 mL x 2). The combined solution was concentrated to afford the tertiary amine product in 92% yield and 99% purity. The tertiary amine was characterized by gas chromatography and ^{1}H NMR.

REFERENCES

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