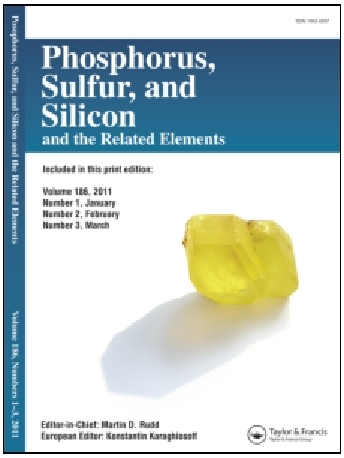

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BENZYTRIPHENYLPHOSPHONIUM BOROHYDRIDE (BTPPB) AS A SELECTIVE REDUCING AGENT FOR REDUCTION OF IMINES, ENAMINES, AND REDUCTIVE AMINATION OF ALDEHYDES WITH PRIMARY AND SECONDRY AMINES IN METHANOL

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BENZYTRIPHENYLPHOSPHONIUM BOROHYDRIDE (BTPPB) AS A SELECTIVE REDUCING AGENT FOR REDUCTION OF IMINES, ENAMINES, AND REDUCTIVE AMINATION OF ALDEHYDES WITH PRIMARY AND SECONDRY AMINES IN METHANOL

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Benzyltriphenyltriphenylphosphonium borohydride (BTPPB) (1) generated as white solid from benzyltriphenylphosphonium chloride and sodium borohydride is found to be a selective and versatile reducing agent. The reagent in methanol is very useful for reduction of imines, enamines and reductive amination of aldehydes.

Keywords: Reduction; Alkylation; Amines; Imines; Enamines

INTRODUCTION

The modification of sodium borohydride has attracted a great deal of attention recently.[1-11] In general, the modification of the usual reducing ability of the sodium borohydride has led to selective reduction of several functional groups, which are otherwise inert to sodium borohydride alone. For instance, the reductions of acid chlorides to aldehydes[2], and alkenes to saturated hydrocarbons[3] can be achieved by use of the combination of sodium borohydride with Cu(I), Co(II) respectively, while such conversions can not be achieved with sodium borohydride alone.

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RESULTS AND DISCUSSION

As an extension of our work in this area[12] we have embarked on a project aimed at selective reduction of imines, enamines and oximes to the corresponding amines. We also tried reductive amination of aldehydes in the presence of ketones. Reduction of imines, enamines and reductive alkylation of primary and secondary amines with aldehydes is widely used in amine synthesis.[12, 13] The Borch method utilizing sodium cyanoborohydride[14] and zincborohydride[15] is, currently, the most popular way to effect this transformation. Other methods include the use of sodium borohydride and trifluroacetic acid[16] or aqueous sulfuric acid,[17] zinc borohydride[18], zinc-modified cyanoborohydride[19], and 1-benzyl-1-azonia-4-azabicyclo[2.2.2]octane tetraborat.[20] Use of sodium cyanoborohydride and zinc cyanoborohydride risks the presence of residual cyanide in the product or work-up system. The presence of acid in the reaction medium restricts its use for molecules containing acid-sensitive in high diastereoselectivity.

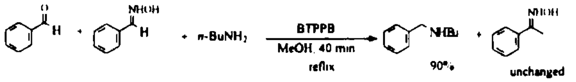
In this paper we wish to report the preparation of benzyltriphenylphoshphonium borohydride (BTPPB) (**1**) and reduction of imines, enamines and reductive amination of primary and secondary amines with aldehydes. This reagent is able to reduce imines and enamines in methanol at room temperature. This reagent is also suitable for reductive amination of aldehydes in the presence of primary and secondary amines in methanol. The reagent is quite soluble in methanol and produces a clear solution, which upon standing at room temperature does not loss its reducing ability. This observation in contrast to what is reported for tetrabutyammonium borohydride (Bu_4NBH_4) which decomposes to the Bu_3N, BuH and BH_3 upon standing in solution[21]. The stability of this reagent in compare to tetrabutyammonium borohydride is the reflection of the presence of phosphonium cation in this reagent, which is more stable than ammonium cation. BTPPB is a white powder, which is prepared by the dropwise addition of an aqueous solution of $NaBH_4$, to an aqueous solution of benzyltriphenylphosphonium chloride at room temperature. Filtration and drying of the precipitate resulted in a white powder, which could be stored for month without loosing its reducing ability (Scheme 1)..

$$Ph_3P^+CH_2PhCl^- + NaBH_4 \xrightarrow{H_2O} Ph_3P^+CH_2PhBH_4^-$$

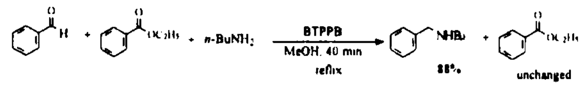
SCHEME 1

The reduction of imines and enamines with this reagent in methanol proceeded smoothly. The reaction was normally completed within 10–40 min at room temperature at room temperature and the corresponding amines were obtained in excellent yields. Under the present conditions, hydrolysis of imines and enamines was not observed. The present procedure does not require pH control, though the reduction with cyanoborohydride occurs at an initial pH of 5 for reduction of imines and enamines.[13] The experimental results are summarized in Tables I. The reductive alkylation of primary and secondary amine with aldehydes with this reagent in methanol at room temperature also proceeded smoothly. The reaction was normally completed within 20–50 min at room temperature and the corresponding amines were obtained in high yields. The experimental results are summarized in Tables II. Very interesting the reductive alkylation of primary and secondary amines with ketones with BTPPB even under refluxing conditions in methanol did not occur at all; therefore this reagent can be used for selective alkylation of primary and secondary amine with aldehyde in the presence of ketones. This reagent can be also used for alkylation of primary and secondary amine with aldehyde in the presence of other functional groups such as ester, oximes and ketones (Eqs. 1–3). In order to evaluate the selectivity of this reagent, the competitive reaction shown in Eqs. 1–3 was carried out. When an equimolar amount of benzaldehyde and *n*-butyl amine and benzophenone was treated with reagent (**1**) (1 mmol), only benzaldehyde was selectively reduced under this condition (eq. 1). Treatment of benzaldehyde and *n*-butyl amine with reagent (**1**)(1 mmol) in the presence of benzaloxime (1 mmol) led to exclusive alkylation of benzaldehyde and *n*-butyl amine (Eq. 2). When we treated benzaldehyde and *n*-butyl amine (1 mmol) with reagent (**1**) in the presence of ethylbenzoate (1 mmol), only the benzaldehyde was selectively aminated (Eq. 3). The selectivity of this reagent is another advantage of this reducing agent over the tetrabutyammonium borohydride (Bu_4NBH_4), which is commercially available.

(Eq 1)

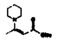
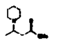
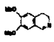
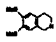
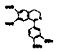
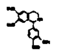
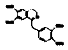
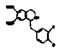
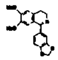
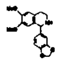
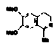
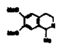


(Eq 2)



(Eq 3)

TABLE I Reduction of Amines and Enamines wit Reducing Agent^{a,b}(I)

Starting Materials	*Reaction Time (min)*	*Yield (%)*	*Product*	*bp/mm Hg mp, °C*
	20	90		57–62/2
	20	86		69–72/3
	30	89		53–57/3.5
	25	78		67–70/4
	40	87		70–73/2
	20	86		235-39/760
	20	90		260–65
	30	79		111–14
	30	80		215–17
	20	92		122–24
	25	85		oil

a. All yields refer to pure isolated products.

b. All of the products were fully characterized by comparing with known compounds and by their IR and ^{1}H NMR spectra.

In conclusion we have discovered a new and useful method for reduction of imines and enamines, and reductive alkylation of primary and secondary amines with aldehydes with BTPPB in methanol. The reagent is cheap and can be stored at room temperature for month without loosing of its activity. This reagent is superior to tetrabutyammonium borohydride (Bu_4NBH_4), which is commercially available, from point of view of stability and selectivity.

TABLE II Reductive amination with reducing agent[a,b] (1)

R^1	R^2	R^3	*Reaction Time (min)*	*Yield (%)*
C_6H_5	H	Cyclohexyl	20	91
C_6H_5	H	$C_6H_4CH_2$	20	98
$3\text{-}NO_2C_6H_4$	H	C_6H_5	35	90
$4\text{-}MeOC_6H_4$	H	C_6H_5	45	88
C_6H_6	H	$2\text{-}BrC_6H_4$	35	89
$2\text{-}MeC_6H_4$	H	C_6H_5	30	94
C_6H_5	H	$2\text{-}MeC_6H_4$	40	90
C_6H_5	H	1-Naphthyl	40	84
C_6H_5	H	$2,6\text{-}(Cl)_2C_6H_3$	35	80
C_6H_5	H	$4\text{-}MeC_6H_4$	40	92
C_6H_5	Me	Cyclohexyl	40	NR
C_6H_5	C_6H_5	Cyclohexyl	40	NR
C_6H_5	Me	$C_6H_4CH_2$	40	NR

a. All yields refer to pure isolated products.

b. All of the products were fully characterized by comparing with known compounds and by their IR and ^1H NMR spectra.

Experimental

All products were identified by comparison with an authentic sample (IR, NMR, mp and bp). All mps. were taken on a Gallenkamp melting apparatus and are uncorrected. Elemental analysis was performed by the Research Institute of Petroleum Industry, Tehran, I.R. Iran,.. ^1H NMR spectra were recorded on a Varian EM-390 NMR Spectrometer operating at 90 MHz, or a Varian Unity 250 Fourier Transform NMR Spectrometer operating at 250 MHz. ^{13}C NMR spectra were recorded on a Varian Unity 400 Fourier Transform NMR Spectrometer operating at 100 MHz The spectra were measured in $CDCl_3$ and CCl_4 using TMS as internal standard. Mass spectra were recorded on a Shimadzu GC-MS-QP 1000PX.

Synthesis of Reducing Agent 1

To a solution of benzyltriphenylphosphonium chloride (19.43 g, 50 mmol) in 50 ml water was added sodium borohydride (1.89 g, 50 mmol) in one portion. The reaction mixture was stirred at room temperature for 30 min. The resulting white solid product was collected, washed with water (10 ml) and dried in a desiccator under vacuum over calcium chloride, to yield 16.38 g (98 %) of white solid product mp 151–153 °C (dec.). ^{1}H NMR: δ 7.90–7.50 (m, 20 H), 4.6 (d, J = 25.6 Hz, CH_2-P). ^{13}C NMR: δ 148.50, 133.20, 130.20, 129.60, 129.40, 128.10, 127.70, 127.2, 108.30 (d, J = 85.5 Hz, P-CH_2). IR (KBr): 1298, 1269, 1098, 1060, 700, 658, 590, 546 cm^{-1}. MS (CI) m/z 368 (100, M$^+$. Anal Calcd for $C_{25}H_{26}BP$: C, 81.52; H, 7.07 %. Found; C, 81.60.80; H, 7.20; %.

Reduction of amines or enamines

The amine or enamine (1 mmol) were added to a stirred solution of reducing agent **1** (1 mmol, 0.37 g) in methanol (10 ml). The mixture was stirred at room temperature until TLC showed complete disappearance of amines or enamines, which required 10–40 min depending on the substrate and then methanol was evaporated under reduced pressure. The residue was dissolved in dichloromethane (10 ml) and washed with water (2x15 ml). The dichloromethane layer was dried over $MgSO_4$. Evaporation of the solvent gave the corresponding amines. The product was purified by column chromatography on neutral alumina using a mixture of ethyl acetate:n-hexane (20:80) as eluent.

Reductive alkylation with primary amines

A mixture of amine (1 mmol) and aldehyde was added to a stirred solution of reducing agent (**1**) (1 mmol, 0.37 g) in methanol (10 ml). The mixture was stirred at room temperature until TLC showed complete disappearance of aldehyde, Which required 20–50 min depending on the substrate, and then the methanol was evaporated under reduced pressure. The residue was dissolved in dichloromethane (10 ml) and washed with water (2x15 ml). The dichloromethane layer was dried over $MgSO_4$. Evaporation of the solvent gave the corresponding amines. The product was purified by column chromatography on neutral alumina using a mixture of ethyl acetate:n-hexane (20:80) as eluent.

Acknowledgements

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