

Note

1-Benzyl-1-azonia-4-azabicyclo[2.2.2]octane tetrahydroborate (BAAOTB) as a selective reducing agent

Abdol Reza Hajipour ^{*a}, Iraj Mohammadpoor -Baltork ^b & Allahkas Rahi

^aCollege of Chemistry, Isfahan University of Technology, Isfahan, Iran.

^bDepartment of Chemistry, Isfahan University, Isfahan, Iran

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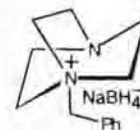
1-Benzyl-1-azonia-4-azabicyclo[2.2.2]octane tetrahydroborate (BAAOTB) **1** generated as white solid from commercially available DABCO and sodium borohydride is found to be a selective and versatile reducing agent. The reagent in *t*-butanol is very useful for reduction of imines, enamines, oximes, reductive amination of aldehydes and ketones and reductive methylation of amines.

The modification of sodium borohydride has attracted a great deal of attention recently.¹⁻¹⁰ In general, the modification of the usual reducing ability of 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 alkenes to saturated hydrocarbons,³ and alkenes to alcohols⁴ can be achieved by use of the combination of sodium borohydride with Cu(I), Co(II) and Sn(IV) respectively, while such conversions can not be achieved with sodium borohydride alone.

As an extension of our work in this area we have embarked on a project aimed at selective reduction of imines and enamines, reduction of oximes to the corresponding hydroxylamines, reductive amination of aldehydes and ketones, and reductive methylation of amines. Reduction of imines and enamines, reductive alkylation of primary and secondary amines with aldehydes and ketones and reductive methylation of aliphatic and aromatic amines with formaldehyde is widely used in amine synthesis.^{11,12} The Borch method utilising sodium cyanoborohydride¹³ and zinc-modified cyanoborohydride¹⁴ being, currently, the most popular way to effect this transformation. Other methods include the use of sodium borohydride and trifluoroacetic acid¹⁵ or aqueous sulfuric acid¹⁶, zinc

borohydride¹⁷ and zinc-modified cyanoborohydride.¹⁸ 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.

Recently we have reported that BAAOTB **1** reduces chiral β -imino sulfoxides to the corresponding β -amino sulfoxides.¹⁹ BAAOTB **1** is a highly selective agent.²⁰ The high chemoselectivity of this reagent encouraged us to focus our investigation for the reduction of other functional groups. This paper describes the reducing properties of **1** for reduction of imines and enamines, reduction of oximes, reductive alkylation of primary and secondary amines with aldehydes and ketones and reductive methylation aromatic amines with formaldehyde.

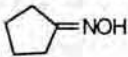
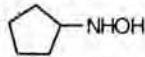
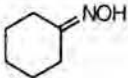
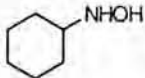


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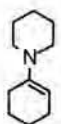
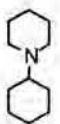
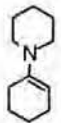
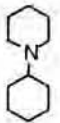
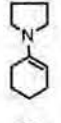
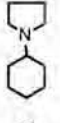


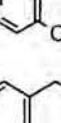

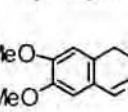
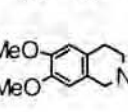
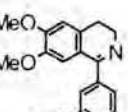
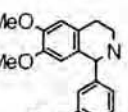
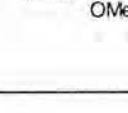
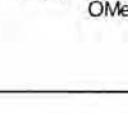
The reduction of imines, enamines and oximes with reducing agent in *t*-butanol proceeded smoothly. The reaction was normally completed within 1-1.5 hr at room temperature and the corresponding amines were obtained in high yields. Under the present conditions, hydrolysis of imines, enamines and oximes 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 and pH of 3-4 for oximes.¹³ In the reduction of oximes with this reagent no trace of overreduction to the amine and dialkylhydroxylamine was observed. The experimental results are summarised in **Tables I and II**. The reductive alkylation of primary and secondary amines with aldehydes and ketones with reducing agent in *t*-butanol proceeded smoothly. The reaction was normally completed within 1.5-2 hr at room temperature and the corresponding amines were obtained in high yields. The experimental results are summarised in **Tables III and IV**.

In conclusion, we have reported a rapid and inexpensive method for the reduction of imines, enamines, oximes, reductive amination of aldehydes and ketones and reductive methylation of amines. The method is superior to the previously reported methods¹⁻¹⁸ in terms of selectivity, yields and purity of the products.

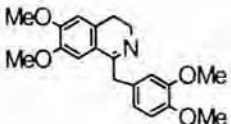
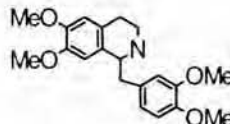
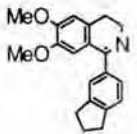
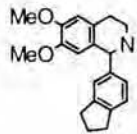
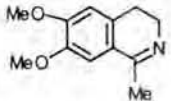
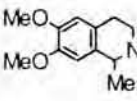
Table I — Reduction of oximes with reducing agent I

Oxime	Hydroxylamine	Reaction period (hr)	Yield (%) ^a	mp °C
$\text{H}_3\text{CCH}_2\text{C}(\text{CH}_3)=\text{NOH}$	$\text{H}_3\text{CCH}_2\text{CH}(\text{CH}_3)\text{NHOH}$	0.5	85	67
$\text{H}_3\text{C}(\text{CH}_2)_2\text{CH}=\text{NOH}$	$\text{H}_3\text{C}(\text{CH}_2)_3\text{NHOH}$	0.5	75	54
$\text{H}_3\text{C}(\text{CH}_2)_5\text{CH}=\text{NOH}$	$\text{H}_3\text{C}(\text{CH}_2)_6\text{NHOH}$	0.6	83	62
$\text{H}_3\text{C}(\text{CH}_2)_6\text{CH}=\text{NOH}$	$\text{H}_3\text{C}(\text{CH}_2)_7\text{NHOH}$	0.6	85	74
		1.0	75	94
		1.0	80	139
$\text{C}_6\text{H}_5\text{CH}=\text{NOH}$	$\text{C}_6\text{H}_5\text{CH}_2\text{NHOH}$	1.2	58	57
$p\text{-NO}_2\text{C}_6\text{H}_4\text{CH}=\text{NOH}$	$p\text{-NO}_2\text{C}_6\text{H}_4\text{CH}_2\text{NHOH}$	1.5	70	127
$\text{C}_6\text{H}_5\text{C}(\text{CH}_3)=\text{NOH}$	$\text{C}_6\text{H}_5\text{C}(\text{CH}_3)\text{NHOH}$	1.5	64	91

^aAll of the products were characterised by comparing with known compounds**Table II** — Reduction of amines and enamines

Compd	Reaction period (hr)	Product	Yield (%) ^a	bp./mmHg or mp, °C
	0.5		84	57-62/2
	0.3		90	69-74/3
	0.5		80	53-57/3.5
	0.3		85	67-70/4
	1.0		73	70-75/2
	0.2		95	235-39/760
	0.2		95	260-65 ^d
	0.2		82	111-14

—contd.

Table II — Reduction of amines and enamines (—Contd.)				
Compd	Reaction period (hr)	Product	Yield (%) ^a	bp/mmHg or mp, °C
	0.3		89	215-17 ^d
	0.2		80	122-24
	0.3		90	Oil

^aAll of the products were characterised by comparing with known compounds

Table III — Reductive methylation of amines with reagent 1			
Amine	Product	Reaction period (hr)	Yield (%) ^a
Benzylamine	<i>N,N</i> -Dimethylbenzylamine	1.2	89
Dodecylamine	<i>N,N</i> -Dimethyldodecylamine	1.0	95
Dicyclohexylamine	<i>N,N</i> -Dimethyldicyclohexylamine	1.3	89
Aniline	<i>N,N</i> -Dimethylaniline	1.5	81
4-Methoxyaniline	<i>N,N</i> -Dimethyl-4-methoxyaniline	1.3	95
2-Nitroaniline	<i>N,N</i> -Dimethyl-2-nitroaniline	1.5	83
<i>p</i> -Toluidine	<i>N,N</i> -Dimethyl- <i>p</i> -toluidine	1.4	88
4-Bromoaniline	<i>N,N</i> -Dimethyl-4-bromoaniline	1.5	85
1-Naphthylamine	<i>N,N</i> -Dimethyl-1-naphthylamine	1.5	81

^aAll of the products were characterised from ¹H NMR and IR data

Table IV — Reductive amination with reducing agent 1

R ¹	R ²	R ³	Reaction period (hr)	Yield (%) ^a
C ₆ H ₄	H	<i>c</i> -C ₆ H ₁₁	1.5	81
C ₆ H ₄	H	C ₆ H ₅ CH ₂	1.5	95
3-NO ₂ C ₆ H ₃	H	C ₆ H ₅	1.5	83
4-MeOC ₆ H ₄	H	C ₆ H ₅	1.5	90
C ₆ H ₅	H	2-BrC ₆ H ₄	1.2	85
2-MeC ₆ H ₄	H	C ₆ H ₅	1.0	90
C ₆ H ₅	H	2-MeC ₆ H ₄	1.2	88
C ₆ H ₅	H	1-naphthyl	2.0	80
C ₆ H ₅	H	2,6-(Cl) ₂ C ₆ H ₃	2.0	74
C ₆ H ₅	H	4-MeC ₆ H ₄	1.6	84
C ₆ H ₅	H	4-MeOC ₆ H ₄	1.5	90
C ₆ H ₅	Me	<i>c</i> -C ₆ H ₁₁	2.0	82
C ₆ H ₄	H	<i>c</i> -C ₆ H ₁₁	1.5	84
C ₆ H ₄	Me	C ₆ H ₅ CH ₂	1.5	74

^aAll yields refer to pure isolated products, fully characterised by IR and ¹H NMR

Experimental Section

Preparation of BAAOTB 1. The reagent was prepared by modification of reported method.²⁰ A mixture of 1-benzyl-4-aza-1-azoniabicyclo[2.2.2]octane bromide²¹ (14.20 g 0.05 mmole), sodium hydroxide (0.07 mmole, 2.80 g) and sodium borohydride (0.06 mmole, 2.28 g) was ground thoroughly in a mortar for 6 hr. The mixture was taken in CH₂Cl₂ (200 mL) and the residue separated by filtration. To the filtrate dried ether (50 mL) was added when white crystal of BAAOTB 1 separated out. They were filtered and the crystals collected, washed with dried ether (2 × 20 mL) and then dried *in vacuo* (0.01 mm Hg), yield 10.68 g (98 %).

Reduction of amines, enamines and oximes. The amine, enamine or oximes (1 mmole) was added to a stirred solution of reducing agent 1 (1 mmole, 0.22 g) in *t*-butanol (10 mL). The mixture was stirred at room temperature until TLC showed complete disappearance of starting material, which required 0.2-1.5 hr depending on the substrate. The mixture was extracted with CH₂Cl₂ (2 × 10 mL), and the solution dried over

MgSO₄. Evaporation of the solvent gave amines or hydroxylamines. The product was purified by column chromatography on silica gel using mixture of ethyl acetate/*n*-hexane (20/80) as eluent.

Reduction alkylation with primary amines. The amine (1 mmole) and aldehyde or ketone (1 mmole) or 37 % aq. formaldehyde (0.4 mL, 5 mmoles), was added to a stirred solution of reducing agent **1** (1 mmole, 0.22 g) in *t*-butanol (15 mL). The mixture was stirred at room temperature until TLC showed complete disappearance of starting material, which required 1.0-2.0 hr depending on the substrate. The mixture was worked-up and purified as above.

Acknowledgement

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