First Report for the Efficient Reduction of Oximes to Amines with Zinc Borohydride in the form of (Pyridine)(tetrahydroborato)zinc Complex

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(Pyridine)(tetrahydroborato)zinc complex, $(Py)Zn(BH_4)_2$, as a stable modification of zinc borohydride can easily reduce a variety of aromatic and aliphatic aldoximes or ketoximes to their corresponding amines in high to excellent yields in refluxing THF.

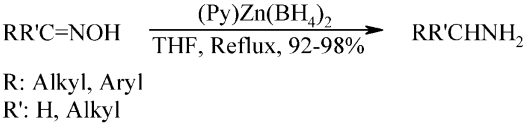
Keywords: Zinc borohydride; Tetrahydroborate; Reduction; Oxime; Amine.

INTRODUCTION

Today's reduction with metal borohydrides is one of the most widely used procedures in organic synthesis. To achieve reductants with different reducing capacities and special selectivity, sodium borohydride as a mild hydride transferring agent has been modified with various methods.[1] Preparation of modified borohydride agents and their applications in organic synthesis has been reviewed recently.[2-5] Zinc tetrahydroborate, $Zn(BH_4)_2$, as a non-conventional hydride transferring agent and modest stable transition metal borohydride has been reported to affect very efficient chemo-, regio- and stereoselective reductions in several complex substrates.[6] This potential reducing agent is a neutral and can be used in a range of aprotic solvents such as ether, THF and DME. High coordination ability of zinc makes zinc tetrahydroborate more selective in its hydride transferring reactions. In spite of this, zinc tetrahydroborate has been used less often than regular reducing agents in laboratories for the reduction of organic compounds, probably because of its non-availability as a commercial reagent, being a freshly prepared solution just prior to use and limitations of handling and storage. The reducing abilities of zinc tetrahydroborate have been reviewed recently.[6,7] In addition to using zinc tetrahydroborate alone as a mild reducing agent, its complexation with some amino or phosphino ligands such as poly[(tetrahydroborato)(η-pyrazine)zinc] complex, $[(pyz)Zn(BH_4)_2]_n$,[8] (1,4-diazabicyclo-[2.2.2]octane)(tetrahydroborato)zinc complex, $[(dabco)Zn(BH_4)_2]$,[4,9] bis(tetrahydroborato)(triphenylphosphine)zinc, $[(Ph_3P)_xZn(BH_4)_2]$ (x = 1,2)[10] and (2,2′-bipyridyl)(tetrahydroborato)zinc complex,[2] $[(bpy)Zn(BH_4)_2]$, is a subject of interest and has been used for different reduction purposes.

In the line of outlined strategies, very recently, we synthesized pyridine zinc tetrahydroborate complex, $(Py)Zn(BH_4)_2$, as a new stable ligand-zinc tetrahydroborate agent and investigated its reducing ability for the reduction of carbonyl compounds, conjugated enones,[11] carboxylic acids, anhydrides[12] and nitro compounds.[13] Now, in order to further explore the utility and generality of this reducing agent for the reduction of other functional groups, the present paper describes the efficient reduction of a variety of aromatic and aliphatic aldoximes or ketoximes to their primary or secondary amines, respectively (Scheme I).

Scheme I



RESULTS AND DISCUSSION

Reduction of oximes is an important synthetic strategy for the preparation of amines and has received much attention over the past few years in both academic and industrial research. Sodium borohydride alone does not reduce oximes under ambient conditions, but efforts have been made to increase its reactivity with additives.[14-16] Modified hydroborates such as BER-$Ni(OAc)_2$[17] and $NaBH_3CN$[18-19] and other reducing agents[20] can also be reduced oximes to their amines, but sometimes reactions are concomitant with some restrictions, e.g.: performing of the reaction in two step procedure

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involving reduction of oxime to an imine which is subsequently reduced to the amine, only reduction with certain substrates such as *o*-alky oxime ethers, *o*-acyl oximes or aryl trifluoromethyl oximes, generation of side products, and finally reaction with only aromatic or aliphatic oximes.

In our ongoing attention to investigate the reducing potential of zinc borohydride for reduction of functional groups in organic synthesis,[2,4,9,11-13] literature review shows that for the use of $Zn(BH_4)_2$ alone or its modifications for the reduction of oximes there haven't been any reports. This subject encouraged us to investigate the reducing potential of zinc borohydride in the form of (pyridine)(tetrahydroborato)zinc complex, $(Py)Zn(BH_4)_2$, for the reduction of oximes. This goal was successfully achieved with the reagent, and so the first ability of zinc borohydride for the reduction of oximes can be shown with this report.

A variety of aromatic or aliphatic aldoximes and ketoximes were reduced to their primary and secondary amines, respectively. The reduction was carried out in refluxing THF and the progress of reactions was followed by TLC. The reaction conditions, reaction times and isolated yield of the products are summarized in Table 1. As is shown, molar ratio of the reagent varies according to the nature of substrate, and it is between 2-4 molar equivalents per one mol of the substrate. Substitution pattern on the aromatic ring has an influence on the reaction rate. The reduction of aryl aldoximes with electron donating substituents like the methoxy group (entry 4) was slow. Aryl aldoxime with a substituted nitro group showed a selectivity and was readily reduced with 2 molar amounts of reagent without affecting the nitro group (entry 5), but with further molar amounts of the reagent the simultaneous reduction of the nitro group took place (entry 6). Aryl aldoximes with chloro and bromo substituents (entries 2, 3 and 8) are also reduced without further reduction of chloro or bromo groups. 1-Naphthalene aldoxime (entry 9) shows further reactivity relative to others with consumption of lower molar equivalents of the reagent. 1,4-Benzoquinone dioxime is also readily reduced to *p*-phenylenediamine in excellent yield (entry 10). The reactivity of aliphatic ketoximes towards the reducing agent was demonstrated with reduction of benzoin oxime to 2-amino-1,2-diphenylethanol and camphor oxime to bornylamine in refluxing THF (entries 11, 12). The work-up procedure is simple and the use of methanolic solution and then extraction with CH_2Cl_2 affords the crude product of amines for further purification with short column chromatography on silica gel. Instability of some amino products such as 3-bromo and 4-nitrobenzylamine (entries 3, 5) leads to recovery of such products as a salt of hydrochloride. The yields of product are high to excellent (92-98%).

CONCLUSION

In conclusion we have shown that $(Py)Zn(BH_4)_2$ reduces a variety of aliphatic or aromatic oximes to their corresponding amines. Selective reduction of oxime over nitro groups, high to excellent yields of products, direct reduction to amines, simple work-up procedure as well as the first report of the ability of zinc borohydride for this transformation could make this procedure an attractive research interest for addition to the present methodologies.

EXPERIMENTAL SECTION

All products were characterized by a comparison with authentic samples (melting or boiling points) or their IR and ^{1}H-NMR spectra. All yields refer to isolated pure products. TLC (silica gel PolyGram SILG/UV-254 plates) accomplished the purity determination of the substrates, products and reactions monitoring.

A Typical Procedure for Reduction of Benzaldehyde Oxime to Benzylamine with $(Py)Zn(BH_4)_2$

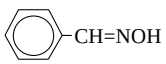
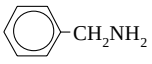
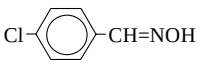
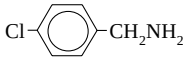
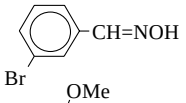
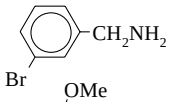
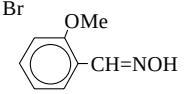
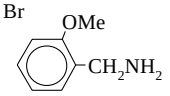
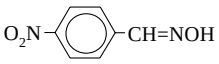
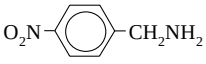
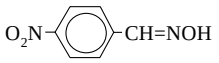
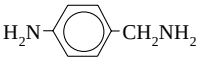
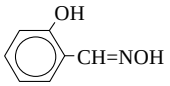
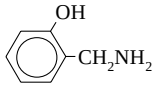
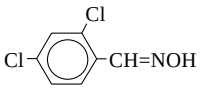
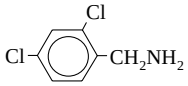
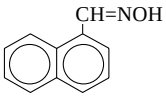
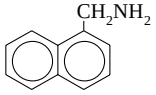
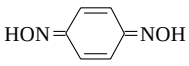
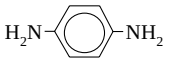
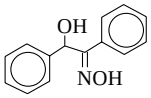
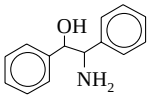
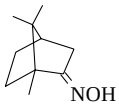
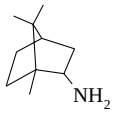
In a round-bottomed flask (15 mL), equipped with a magnetic stirrer and condenser, a solution of benzaldehyde oxime (0.121 g, l mmol) in THF (5 mL) was prepared. Reducing agent (0.522 g, 3 mmol) was then added and the mixture was stirred under reflux condition for 3 h. TLC monitored the progress of the reaction (eluent; CCl_4/Et_2O: 5/2). After completion of the reaction, aqueous MeOH (10 mL) was added to the reaction mixture and stirred for an additional 10 min. The mixture was extracted with CH_2Cl_2 (3×10 mL) and dried over anhydrous sodium sulfate. Evaporation of the solvent and short column chromatography of the resulting crude material over silica gel (eluent; CCl_4/Et_2O: 5/3) affords pure liquid benzylamine (0.1 g, 94% yield, Table 1).

Spectral data of the products are as follows:

Benzylamine (**entry 1**): δ_H (60 MHz, $CDCl_3$): 7.3 (5H, s), 3.9 (2H, s), 1.4 (2H, s). IR (υ, neat): 3367, 3278, 3039, 2940, 2857, 1600, 1492, 1450, 1388, 1052, 1025, 854, 780, 775, 730, 695.

4-Chlorobenzylamine (**entry 2**): δ_H (60 MHz, $CDCl_3$): 7.2 (4H, s), 3.8 (2H, s), 1.3 (2H, s). IR (υ, neat): 3380, 3290, 3180, 3040, 2925, 2860, 1587, 1900, 1600, 1495, 1408, 1380, 1095, 1020, 860, 815, 720, 650.

Table 1. Reduction of oximes to amines with $(Py)Zn(BH_4)_2$[a]

Entry	Substrate	Product	Molar Ratio Reag./Subs.	Time (h)	Yield (%)[b]	Mp or Bp (°C)	
						Found	Reported
1			3:1	3	94	183-184	184-185[21a]
2			3:1	2.8	96	215-216	215[21a]
3[c]			3:1	2.3	94	219-221	218-222[21a]
4			4:1	6	95	226/724	227/724 mmHg[21a]
5[c,d]			2:1	1.5	93	266	~265[21a]
6			4:1	4.3	95	101/0.05	101/0.05 mmHg[21a]
7			3:1	0.5	96	129-130	129[21b]
8			3:1	4	98	257-259	258-260[21a]
9			2:1	0.4	98	290-292	290-293[21a]
10			3:1	1	95	143-144	141-143[21a]
11			3:1	3	94	142-144	142-145[21a]
12			3:1	1.5	92	160-162	160-163[21a]

[a] All reactions were performed in THF under reflux. [b] Yields refer to isolated pure products. [c] The product was recovered as salt of hydrochloride. [d] Decomposition point.

3-Bromobenzylamine hydrochloride (**entry 3**): δ_H (60 MHz, $CDCl_3$ + DMSO-d_6): 8.8 (3H, bs), 7.75 (1H, s), 7.6-7.4 (2H, m), 7.3 (1H, t), 4.05 (2H, s). IR (υ, KBr): 2963, 2935, 2852, 1600, 1582, 1455, 1383, 1212, 1110, 1091, 1005, 963, 905, 877, 835, 790, 696.

2-Methoxybenzylamine (**entry 4**): δ_H (60 MHz, $CDCl_3$): 7.3-6.6 (4H, m), 3.75 (2H, s), 3.7 (3H, s), 1.6 (2H, s). IR (υ, neat): 3385, 3300, 3200, 3000, 2940, 2830, 1600, 1580, 1500, 1460, 1440, 1390, 1320, 1295, 1250, 1180, 1110, 1050, 1040, 900, 820, 760, 730.

4-Nitrobenzylamine hydrochloride (**entry 5**): δ_H (60 MHz, DMSO-d_6): 8.9 (3H, bs), 8.3 (2H, d), 7.8 (2H, d), 4.3 (2H, s).

4-Aminobenzylamine (**entry 6**): δ_H (60 MHz, $CDCl_3$): 7.1 (2H, d), 6.6 (2H, d), 3.8-3.5 (2H, b), 3.7 (2H, s), 1.5-1.3 (2H, b). IR (υ, neat): 3420, 3360, 3205, 3010, 2930, 2850, 1615, 1520, 1440, 1290, 1180, 1130, 1085, 1030, 880, 825.

2-Hydroxybenzylamine (**entry 7**): δ_H (60 MHz, $CDCl_3$): 7.25-6.8 (4H, m), 3.7 (2H, s), 1.8 (2H, s).

2,4-Dichlorobenzylamine (**entry 8**): δ_H (60 MHz,

$CDCl_3$): 7.4-7.1 (3H, m), 3.9 (2H, s), 1.5 (2H, s). IR (υ, neat): 3390, 3300, 3090, 3070, 2940, 2880, 1590, 1562, 1470, 1392, 1260, 1200, 1098, 1100, 1050, 865, 820, 732, 740, 715, 700, 650.

1-Naphthylmethylamine (**entry 9**): δ_H (60 MHz, $CDCl_3$): 7.9-7.2 (7H, m), 4.0 (2H, s), 1.3 (2H, s). IR (υ, neat): 3380, 3295, 3190, 3050, 2900, 2880, 2850, 1607, 1510, 1460, 1395, 1270, 1162, 966, 833, 790, 772, 735, 699.

***p*-Phenylenediamine** (**entry 10**): δ_H (60 MHz, DMSO-d_6): 6.7 (4H, s), 3.7-2.7 (4H, b). IR (υ, KBr): 3385, 3300, 3200, 2960, 2930, 2850, 1630, 1520, 1455, 1370, 1310, 1263, 1140, 845, 800, 730.

2-Amino-1,2-diphenylethanol (**entry 11**): δ_H (60 MHz, $CDCl_3$): 7.35-7.1 (10H, m), 4.7 (1H, d), 4.1 (1H, d), 1.6-1.2 (2H, b). IR (υ, KBr): 3340, 3285, 3090, 2960, 2930, 2850, 1595, 1462, 1380, 1352, 1290, 1222, 1090, 1030, 1010, 910, 760, 700, 590.

Bornylamine (**entry 12**): δ_H (60 MHz, DMSO-d_6): 2.9-2.8 (1H, m), 2.2-0.5 (9H, m), 0.85 (3H, s), 0.65 (6H, s).

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