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One-Pot Sequence for Reductive-Acetylation of Carbonyl Compounds with (N-Methylimidazole)(tetrahydroborato)zinc Complex

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Reductive-acetylation of variety of aliphatic and aromatic aldehydes and ketones, α,β-unsaturated carbonyl compounds are examined efficiently with (N-methylimidazole)(tetrahydroborato)zinc complex, $[Zn(BH_4)_2(nmi)]$, under mild condition in THF at room temperature or reflux conditions. The corresponding acetates were obtained in excellent yields (90-98 %).

Key Words: Reductive-acetylation, Zinc borohydride, Carbonyl compounds, N-Methylimidazole.

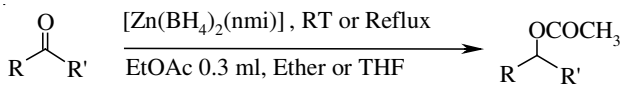
INTRODUCTION

During the past decades, sodium borohydride is always playing an important role in modern organic synthesis[1]. This reagent is a relatively mild reducing agent and it is mostly used for the reduction of aldehydes and ketones specially in protic solvents. In order to control the reducing power of the reagent, hundreds of substituted boron hydrides have been introduced in chemical literature and many are now commercially available. The most common modifications that have been made on sodium borohydride are described by different methods, such as: hydride exchange, cation exchange, cation and hydride exchange, combining borohydrides with metals, metal salts, metal hydrides, Lewis acids, solid supports, attaching asymmetric ligands, using mixed solvents containing methanol, ligand-metal exchange and by quaternary ammonium and phosphonium exchange[2].

$LiBH_4$, $Ca(BH_4)_2$ and $Zn(BH_4)_2$[3] are the modified borohydride agents which have a better solubility in aprotic solvents, so their uses and applications are of the interest in organic synthesis. Among these reagents, zinc borohydride is unique because of (a) Zn^{2+} is a soft Lewis acid in comparison to Ca^{2+}, Li^+ and Na^+ which are hard acids and (b) better coordination ability of Zn^{2+} which is imparting selectivity in hydride transferring reactions. Zinc borohydride is moderately stable in ethereal solution and found more applications in organic synthesis[4]. However, because of its requirement for storage in a cold place and instability in solid state or in solution for a long time, it should always be used as its freshly prepared ethereal solutions which is puts some restriction on its uses. Recently, new stable modifications of zinc borohydride in the form of tertiary amino or phosphino ligand complexes such as polytetrahydro[(1,4-η)pyrazine]boratozinc, $[(Pyz)Zn(BH_4)_2]_n$[5], (1,4-diazabicyclo-

[2.2.2]octane)tetra-hydroboratozinc complex[2,6], [(dabco)$Zn(BH_4)_2$] and mono or (bistriphenylphosphine)zinc tetra-hydroborate[7], [$(Ph_3P)_xZn(BH_4)_2$] (X = 1, 2), have been introduced and their applications for the reduction of different functional groups have been reviewed.

In connection to these developments we synthesized the new stable N-methylimidazole complex of zinc borohydride as [$Zn(BH_4)_2$(nmi)] and investigated it's reducing ability[8]. During the course of study on the reduction of carbonyl compounds with this reagent, we evaluate their reductions in different solvents. When benzaldehyde as a model compound is reduced with the reagent in ethyl acetate, its reduction was accompanied by concomitant alcoholysis of ethyl acetate and the benzyl acetate is obtained in moderately yield. This result prompted us to investigate the ability of this new reducing agent for one-pot reductive-acetylation of carbonyl compounds. Now we wish to report an efficient method for the reductive-acetylation of aliphatic and aromatic aldehydes and ketones, α,β-unsaturated carbonyl compounds in excellent yields of products (**Scheme-I**).



R : Alkyl, Aryl; R' : H, Alkyl, Aryl

Scheme-I

EXPERIMENTAL

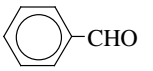
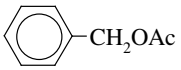
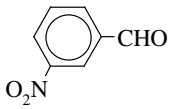
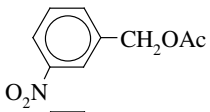
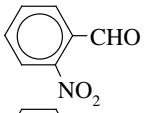
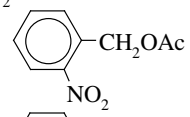
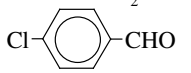
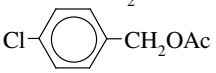
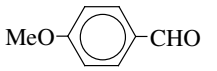
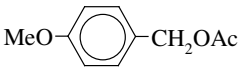
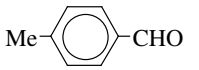
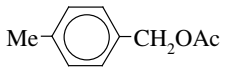
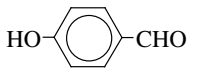
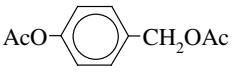
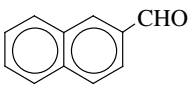
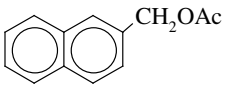
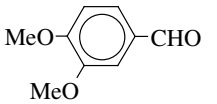
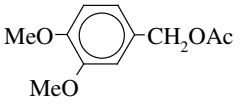
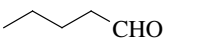
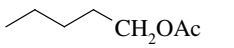
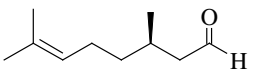
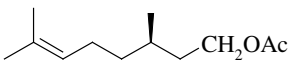
All reagents and substrates were purchased from commercial sources with the best quality and were used without further purification. IR and ^1H NMR spectra were recorded on Thermo Nicolet Nexus 670 FT-IR and 300 MHz Bruker Avance spectrometers, respectively. The products were characterized by a comparison with authentic samples (melting or boiling points) and their ^1H NMR or IR spectra. All yields refer to isolated pure products. TLC was applied for the purity determination of substrates, products and reaction monitoring over silica gel 60 F_{254} aluminum sheet.

Preparation of (N-methylimidazole)(tetrahydroborato)zinc complex [$Zn(BH_4)_2$(nmi)]: An ethereal solution of $Zn(BH_4)_2$ (0.16 M, 250 mL) was prepared from $ZnCl_2$ (5.452 g, 0.04 mol) and $NaBH_4$ (3.177 g, 0.084 mol) according to an established procedure in the literature[8,9]. Then, N-methylimidazole (3.280 g, 0.04 mol) in ether (50 mL) was added drop wise to the ethereal solution of $Zn(BH_4)_2$ and stirred for 0.5 h. Evaporation of the solvent under vacuum at room temperature gave [$Zn(BH_4)_2$(nmi)] in almost quantitative yield (6.73 g, 95 %)[8] in powder form.

A typical procedure for reductive-acetylation of benzaldehyde to benzyl acetate with [$Zn(BH_4)_2$(nmi)]: In a round-bottomed flask (10 mL), equipped with a magnetic stirrer, a solution of benzaldehyde (0.106 g, 1 mmol) in ether (4 mL) and 0.3 mL ethyl acetate was prepared. The reducing agent (0.178 g, 1 mmol) was

added and the mixture was stirred magnetically at room temperature for 1 h. TLC monitored the progress of the reaction (eluent; CCl_4/Et_2O: 5/2). After completion of the reaction, distilled water (5-10 mL) was added and magnetically stirred for 10 min. The mixture was extracted with CH_2Cl_2 (3 × 10 mL) and was then dried over the anhydrous sodium sulfate. Evaporation of the solvent followed by chromatography of the resulting crude material over silica gel by the eluent of CCl_4/Et_2O: 5/2 affords pure benzyl acetate (0.142 g, 95 % yield, Table-1).

TABLE-1
REDUCTIVE ACETYLATION OF ALDEHYDES WITH $[Zn(BH_4)_2(nmi)]$[a]

Entry	Substrate	Product	Molar Ratio Reag./Subs.	Time (h)	Yield (%)[b]
1			1	1	95
2			2	2.5	93
3			2	3	96
4			2	2	98
5			1	1.8	97
6			1	2	96
7			2	2.5	96
8			1	1.5	93
9			1	0.6	94
10			1	0.2	95
11			1	0.2	96

[a] All reactions were performed in ether accompanied with 0.3 ml ethyl acetate at room temperature.
[b] Yields referred to isolated products.

RESULTS AND DISCUSSION

One-pot reductive-acetylation of aldehydes and ketones is the generally way for transformation of these compounds to their acetates. The methods are reported for this achievement include the using of Zn/Ac_2O/tertiary amines[10], Zn/Ac_2O/pyridine[11], $Zn/Ac_2O/NaOAc$[12], acetyl chloride/Bu_3SnH[13] and $NaBH_4$/ethyl acetate[14]. Low yields of the products, drastic reaction conditions, long reaction times and low selectivity of the reagents are the drawbacks of reported methods. The application of poly(4-vinyl) supported zinc borohydride for this transformation has been reported[15]. This stable polymeric analogue of zinc borohydride selectively acetylates aldehydes *versus* ketones, but the yields of the corresponding products are moderately low.

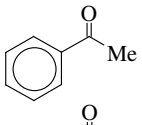
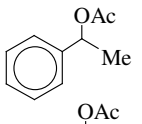
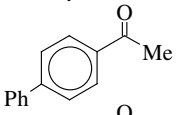
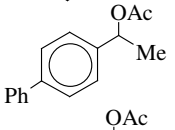
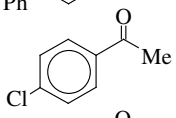
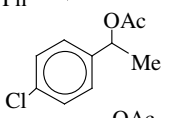
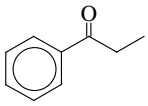
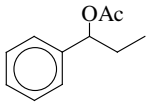
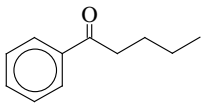
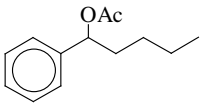
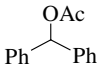
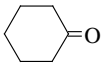
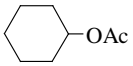
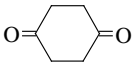
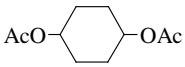
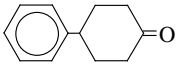
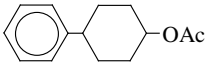
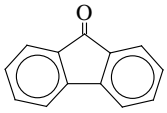
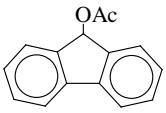
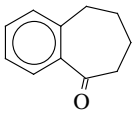
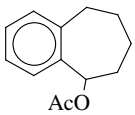
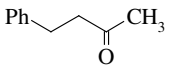
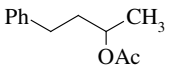
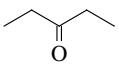
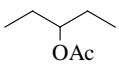
With our preliminary studies and investigation of new synthetic methodology for one-pot reductive-acetylation of carbonyl compounds, we decided to apply and optimize our newly synthesized reducing agent for this transformation. N-Methyl-imidazole zinc tetrahydroborate complex is a solid stable compound and can be stored for months without losing its activity. It is not hydroscopic or light sensitive and its preparation is easy and could be formed in two consecutive steps. Formation of zinc borohydride by the exchange reaction of zinc chloride and sodium borohydride in dry ether followed by the 1:1 complexation of ethereal solution of N-methyl-imidazole with zinc borohydride produces almost quantitative yield of the reagent. So, we optimized the reaction condition and found that ether or THF in mixing with 0.3 mL ethyl acetate are the solvent of choice for excellent efficiencies. This transformation is performed with 1-4 molar equivalents of the reagent at room temperature or under reflux conditions and in good to excellent yields of the products. The facile reductive-acetylation of variety of carbonyl compounds are summarized in Tables 1-3.

As it is shown in Table-1, simple substituted aromatic and aliphatic aldehydes are efficiently converted to their acetates with 1-2 molar equivalents of the reagent in ether accompanied with 0.3 mL ethyl acetate at room temperature. The corresponding acetates were obtained in excellent yields. Generally the rate of transformation for aliphatic aldehydes is faster than the aromatic compounds. Under the defined condition phenolic group is also susceptible for acetylation and our attempts for selective acetylation of carboxaldehyde or phenolic groups were unsatisfactory.

Our investigation in reductive-acetylation of ketones with this reducing agent shows that their reductions are carried out in THF accompanied with 0.3 mL ethyl acetate at room temperature or under reflux condition (Table-2). These reactions need to higher molar ratio of the reagent (2-4 molar equivalents) and moderately longer reaction times in comparison with those required for transformation of aldehydes.

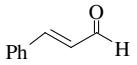
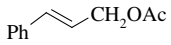
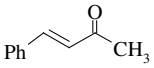
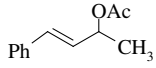
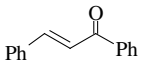
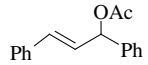
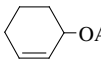
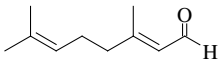
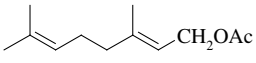
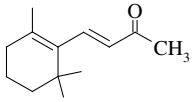
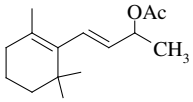
Regioselective reductive-acetylation of α,β-unsaturated carbonyl compounds were also efficiently examined in THF in mixing with 0.3 mL of ethyl acetate. This transformation needs to 1-3 molar equivalents of the reagent and aldehydes are

TABLE-2
REDUCTIVE ACETYLATION OF KETONES WITH $[Zn(BH_4)_2(nmi)]$[a]

Entry	Substrate	Product	Molar Ratio Reag./Subs.	Time (h)	Yield (%)[b]
1			3	3	95
2			3	4	93
3			3	5	97
4			3	5	98
5			3	3	95
6			3	8	91
7			2	0.30	93
8			4	1	94
9			2	1	90
10			4	8	98
11			3	3	90
12			2	1	92
13			2	1	96

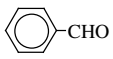
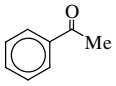
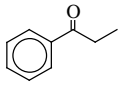
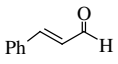
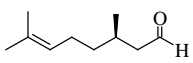
[a] All reactions were performed in THF accompanied with 0.3 ml ethyl acetate under reflux conditions.
[b] Yields referred to isolated products.

TABLE-3
REDUCTIVE ACETYLATION OF α,β-UNSATURATED CARBONYL COMPOUNDS WITH $[Zn(BH_4)_2(nmi)]$[a]

Entry	Substrate	Product	Condition	Molar Ratio Reag./Subs.	Time (h)	Yield (%)[b]
1			RT	1	1	97
2			Reflux	3	3	96
3			Reflux	3	6	93
4			Reflux	2	2	92
5			RT	1	1	95
6			Reflux	2	4	95

[a] All reactions were performed in THF accompanied with 0.3 ml ethyl acetate.
[b] Yields referred to isolated products. RT = Room temperature

TABLE-4
COMPARISON OF REDUCTIVE ACETYLATION OF CARBONYL COMPOUNDS WITH $[Zn(BH_4)_2(nmi)]$[a] AND OTHER BOROHYDRIDE SYSTEMS

Entry	Substrate	Molar Ratio (Reag./Subs.), Time (h) and Yield (%)		
		I	II[14]	III[15]
1		(1:1)(1)(95)	(1:1)(7)(67)	(1:1)(15)(90)
2		(3:1)(3)(95)	(1:1)(7)(80)	(1:1)(20)(5)
3		(3:1)(5)(98)	(1:1)(15)(86)	–
4		(2:1)(0.3)(93)	(1:1)(76)(86)	(1:1)(20)(8)
5		(1:1)(1)(97)	–	(1:1)(18)(80)
6		(1:1)(1)(95)	–	(1:1)(18)(80)

[I][Zn(BH4)2(nmi)]; [II]NaBH4/EtOAc; [III]Poly(4-vinylpyridine) supported Zn(BH4)2

converted to their acetates at room temperature and ketones under reflux conditions (Table-3). To show the efficiency of this reagent, we compared some of our results with those of achieved by $NaBH_4$/EtOAc[14] and poly(4-vinylpyridine) supported $Zn(BH_4)_2$[15] systems (Table-4).

Conclusion

In conclusion, we have shown the one-pot sequence reductive-acetylation of a variety of aldehydes and ketones with $[Zn(BH_4)_2(nmi)]$. Also, in view points of high efficiencies and regioselectivity, mild and neutral reaction conditions, easy work-up of the reaction mixture are the advantages of the present method and can be make it as a useful addition to the present methodologies. It is believed that this reagent can be considered as a suitable reagent for one-pot sequence reductive-acetylation of various kinds of carbonyl compounds.

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