Reductive Acetylation of Carbonyl Compounds to Acetates with Pyridine Zinc Borohydride

Behzad Zeynizadeh,* Davood Setamdideh, and Fariba Faraji

*Department of Chemistry, Faculty of Sciences, Urmia University, Urmia 57159-165, Iran. *E-mail: bzeynizadeh@gmail.com*
Received June 26, 2007

Reductive acetylation of a variety of carbonyl compounds such as aldehydes, ketones and α,β-unsaturated enals/enones was carried out efficiently with pyridine zinc borohydride, $(Py)Zn(BH_4)_2$, in a mixture of THF-EtOAc at room temperature or under reflux condition. The corresponding acetates were obtained in high to excellent yields. In addition, chemoselective reductive acetylation of aldehydes over ketones was achieved perfectly with the reagent at room temperature.

Key Words : Zinc borohydride, Reductive acetylation, Carbonyl compounds, Pyridine

Introduction

Acetylation of carbonyl compounds is generally achieved via reduction followed by the acetylation. However, the literature review shows that direct reductive acetylation of such compounds was rarely studied. Zn/Ac_2O/tertiary amines,[1] Zn/Ac_2O/pyridine,[2] Zn/Ac_2O/NaOAc,[3] CH_3COCl/Bu_3SnH,[4] and lanthanide complexes/isopropenyl acetate[5] are the methods which have been reported for this transformation. Moreover, the combination systems of borohydrides have been also reported for one-pot reductive acetylation of carbonyl compounds. The protocol of $NaBH_4$/EtOAc[6] was the first report in this subject; however, the method described reductive acetylation of few carbonyl compounds to their acetates in moderate yields. Moreover, this method was accompanied with the reduction, producing carbinols as side products. Tamami *et al*. developed the title reaction by the application of poly(4-vinylpyridine) supported $Zn(BH_4)_2$ for chemoselective reductive acetylation of aldehydes over ketones.[7] Though the method is successful in its chemoselectivity, however, long reaction times and moderate yields of products are disadvantages of this method.

Recently, we reported pyridine zinc borohydride complex, $(Py)Zn(BH_4)_2$, as a bench-top and versatile reducing agent in organic synthesis.[8-12] In the course of our study to discover the new applications of this reagent, we found that the reduction of benzaldehyde with the reagent in ethyl acetate provided benzyl alcohol and benzyl acetate. Encouraged by the result, we undertook the study for one-pot reductive acetylation of a variety of carbonyl compounds, such as aldehydes, ketones and α,β-unsaturated enals/enones, to acetates using the reagent (Scheme 1).

$$RR'CO \xrightarrow[THF\text{-}EtOAc]{(Py)Zn(BH_4)_2} RR'CH(OAc)$$

Scheme 1

Results and Discussion

We initially compared the reductive acetylation reaction of benzaldehyde in various solvents at room temperature (Table 1). When benzaldehyde (1 mmol) was reacted with $(Py)Zn(BH_4)_2$ (1 mmol) in ethyl acetate, the reaction provided benzyl alcohol and benzyl acetate in ratio of 40:60, respectively. By changing solvent systems, the ratio of the formation of benzyl acetate was dramatically improved. Among the examined solvent systems, THF-EtOAc (3:0.3 mL for 1 mmol scale) system provided the best result to give only benzyl acetate in 95% yield (entry 2). For other aromatic and aliphatic aldehydes, the same reaction was carried out under the same conditions. As shown in Table 2, the reactions were completed by 1-3 molar equivalents of the reagent within 0.3-3.6 h to give the corresponding acetates as sole products in 79-98% yields. *o*-Phthalaldehyde with two aldehyde moieties was also successfully converted to the corresponding acetate in 92% yield (Table 2, entry 11). Next, the same reaction was applied to ketones. Thus, the reaction of acetophenone (1 mmol) was carried out with a large excess of the reducing agent (4 mmol) in THF-EtOAc (3:0.3 mL) under refluxing conditions. The reaction gave α-phenylethyl acetate in 94% yield within 10 h. Similarly, reductive acetylation of other ketones was completed by 2-4 molar equivalents of this reagent within 0.3-10 h under the identical conditions to give the corresponding acetates as sole products in high to excellent yields (Table 3).

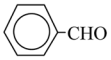
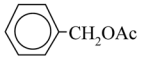
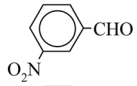
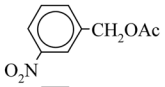
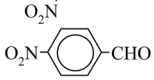
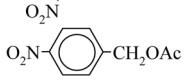
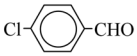
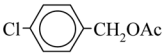
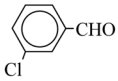
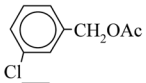
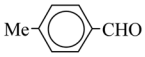
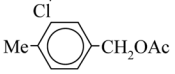
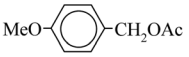
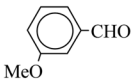
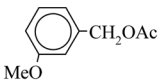
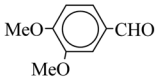
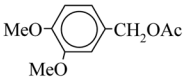
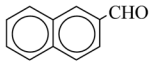
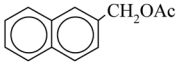
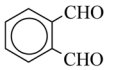
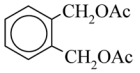
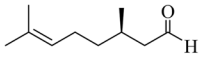
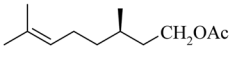
This method also was successful for the regioselective

Table 1. Optimization of Solvent System in Reductive Acetylation of PhCHO with $(Py)Zn(BH_4)_2$[a]

Entry	Solvent System (mL)	Time (h)	Alcohol + Ester (%)
1	EtOAc (3)	1.2	40 + 60
2	THF-EtOAc (3:0.3)	2	0 + 100
3	THF-EtOAc (2:0.2)	2	20 + 80
4	THF-EtOAc (1:0.1)	4	70 + 30
5	CH_3CN-EtOAc (3:0.3)	3	20 + 80

[a]The reactions were acarried out with the molar ratio of PhCHO: $(Py)Zn(BH_4)_2$ (1:1) at room temperature.

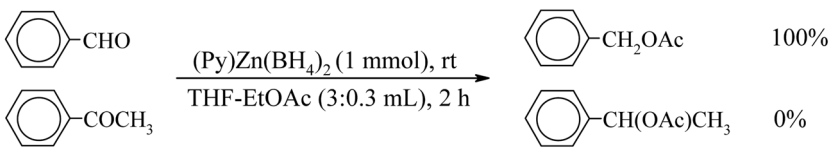
Table 2. Reductive Acetylation of Aldehydes with $(Py)Zn(BH_4)_2$[a]

Entry	Substrate	Product	Molar Ratio Reag./Subs.	Time (h)	Yield (%)[b]	Ref.
1			1:1	2	95	13
2			2:1	3.6	93	14
3			2:1	3	95	15
4			2:1	2.3	98	15
5			2:1	3	97	15
6			2:1	1	98	16
7			2:1	1.5	97	16
8			2:1	0.7	95	16
9			2.5:1	0.3	94	17
10			2:1	1.8	98	18
11			3:1	0.3	92	19
12	$CH_3CH_2CH_2CHO$	$CH_3CH_2CH_2CH_2OAc$	1:1	0.3	79	13
13			1:1	0.3	88	20

[a]All reactions were carried out with 1 mmol scale of substrate in a mixture of THF-EtOAc (3:0.3 mL) at room temperature. [b]Yields refer to isolated pure products.

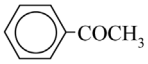
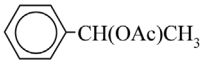
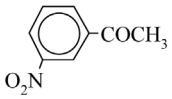
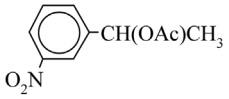
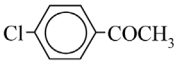
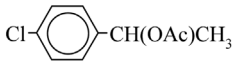
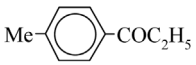
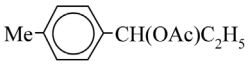
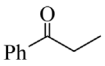
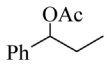
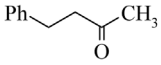
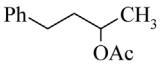
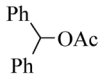
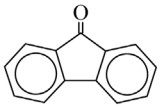
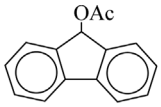
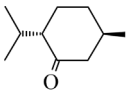
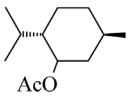
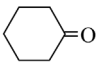
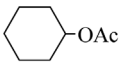
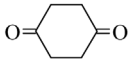
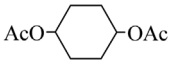
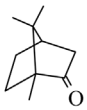
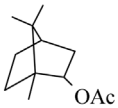
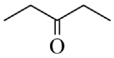
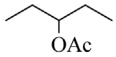
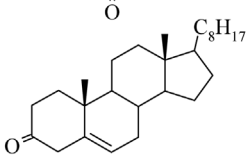
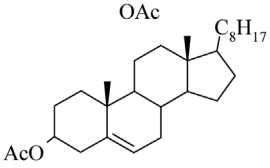
reductive acetylation of α,β-unsaturated carbonyl compounds (Table 4). Finally, based on the results in Tables 2 and 3, we studied the chemoselective reductive acetylation of aldehydes in the presence of ketones. We first carried out the competitive reductive acetylation by reacting benzaldehyde in the presence of an equimolar amount of acetophenone with one molar equivalent of the reducing agent at room temperature. It was found that benzaldehyde was selectively acetylated over acetophenone with a perfect selection (Scheme 2). As shown in Table 5, all examined aldehydes were chemoselectively converted over ketones into the corresponding acetates (Table 5). To show the efficiency of this reagent, we compared some of our results with those of achieved by $NaBH_4$/EtOAc[6] and poly(4-vinylpyridine) supported $Zn(BH_4)_2$[7] systems. Among those, $(Py)Zn(BH_4)_2$ provided the best results (Table 6). The exact mechanism of this synthetic method is unclear so far. However, we think that the following mechanistic pathway plays a role in the direct reductive acetylation of carbonyl compounds with the reagent (Scheme 3).

In conclusions we have shown the one-pot reductive acetylation of a variety of aldehydes and ketones with $(Py)Zn(BH_4)_2$. Also, the chemoselective reductive acetylation of aldehydes in the presence of ketones with this reducing agent was perfectly achieved. In view points of high efficiency, regio- and chemoselectivity of the reactions, mild reaction conditions and the easy work-up procedure, we believe that this reagent can be considered as a suitable and perfect reagent for one-pot reductive acetylation of various kinds of carbonyl compounds.

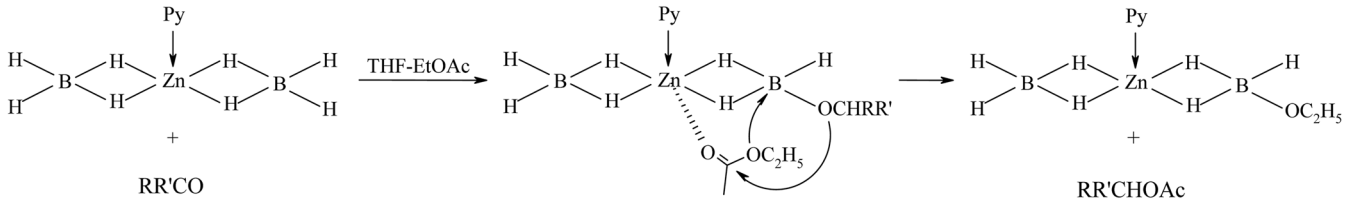


Scheme 2

Table 3. Reductive Acetylation of Ketones with $(Py)Zn(BH_4)_2$[a]

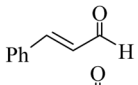
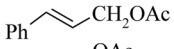
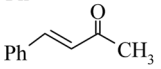
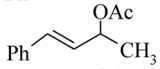
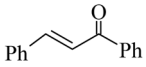
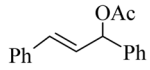
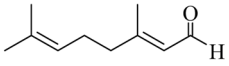
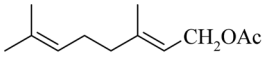
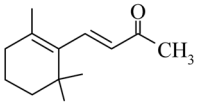
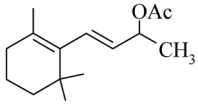
Entry	Substrate	Product	Molar Ratio Reag./Subs.	Time (h)	Yield (%)[b]	Ref.
1			4:1	10	94	21
2			4:1	2	96	22
3			4:1	2.5	97	23
4			4:1	5	96	24
5			3:1	1.6	95	25
6			2:1	0.3	95	13
7			4:1	10	98	15
8			4:1	8	96	23
9			4:1	2	95	26
10			2:1	0.3	80	26
11			3:1	0.4	83	27
12			4:1	2	90	28
13			2:1	0.3	75	29
14			4:1	4	96	30

[a]All reactions were carried out with 1 mmol scale of substrate in a mixture of THF-EtOAc (3:0.3 mL) under reflux conditions. [b]Yields refer to isolated pure products.



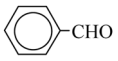
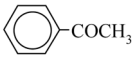
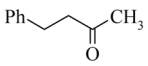
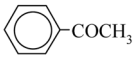
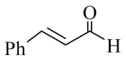
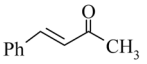
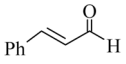
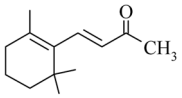
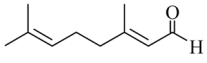
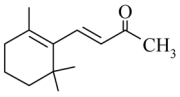
Scheme 3

Table 4. Reductive Acetylation of α,β-Unsaturated Carbonyl Compounds with $(Py)Zn(BH_4)_2$[a]

Entry	Substrate	Product	Condition	Molar Ratio Reag./Subs.	Time (h)	Yield (%)[b]	Ref.
1			rt	1:1	0.7	93	31
2			reflux	3:1	3.5	94	32
3			reflux	4:1	12	92	24
4			rt	2:1	0.6	89	13
5			reflux	3:1	10	90	33

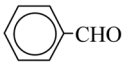
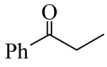
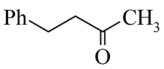
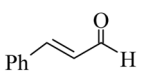
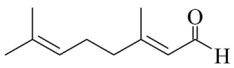
[a]All reactions were carried out with 1 mmol scale of substrate in a mixture of THF-EtOAc (3:0.3 mL). [b]Yields refer to isolated pure products.

Table 5. Competitive Reductive Acetylation of Carbonyl Compounds with $(Py)Zn(BH_4)_2$[a]

Entry	Substrate **1**	Substrate **2**	Molar Ratio[b]	Condition	Time (h)	Conv. 1 (%)[c]	Conv. 2 (%)[c]
1			1:1:1	rt	2.2	100	0
2			2:1:1	reflux	0.4	100	0
3			1:1:1	rt	0.8	96	< 5
4			1:1:1	rt	0.8	96	< 5
5			2:1:1	rt	0.7	97	< 4

[a]All reactions were carried out with 1 mmol scale of substrate in a mixture of THF-EtOAc (3:0.3 mL). [b]Molar ratio as Reag./Subs. 1/Subs. 2. [c]Conversions refer to TLC monitoring and isolated pure products.

Table 6. Comparison of Reductive Acetylation of Carbonyl Compounds with $(Py)Zn(BH_4)_2$ and Other Borohydride Systems

Entry	Substrate	Molar Ratio (Reag./Subs.), Time (h) and Yield (%)		
		I	II[6]	III[7]
1		(1:1)(2)(95)	(1:1)(7)(67)	(1:1)(15)(90)
2		(4:1)(10)(94)	(1:1)(7)(80)	(1:1)(20)(5)
3		(3:1)(1.6)(95)	(1:1)(15)(86)	–
4		(2:1)(0.3)(95)	(1:1)(10)(89)	–
5		(2:1)(0.3)(80)	(1:1)(7)(86)	(1:1)(20)(8)
6		(1:1)(0.7)(93)	–	(1:1)(20)(80)
7		(2:1)(0.6)(89)	–	(1:1)(18)(80)

[I]$(Py)Zn(BH_4)_2$; [II]$NaBH_4$/EtOAc; [III]Poly(4-vinylpyridine) supported $Zn(BH_4)_2$

Experimental Section

General. Pyridine zinc borohydride was prepared by the reported procedure.[8] All reagents and substrates were purchased from Merck and Fluka companies with the best quality and they were used without further purification. IR and ^{1}H NMR spectra were recorded on Thermo Nicolet Nexus 670 FT-IR and 300 MHz Bruker Avance spectrometers, respectively. The products were characterized by their ^{1}H NMR or IR spectra and comparison with the reported date in literature. All yields refer to isolated pure products. TLC over silica gel 60 F_{254} aluminum sheets was applied for the purity determination of the substrates, products and for reaction monitoring

A Typical Procedure for Reductive Acetylation of Benzaldehyde to Benzyl Acetate with (Py)Zn(BH$_4$)$_2$. In a round-bottomed flask (10 mL), equipped with a magnetic stirrer, a solution of benzaldehyde (0.106 g, l mmol) in a mixture of THF-EtOAc (3:0.3 mL) was prepared. (Py)-$Zn(BH_4)_2$ (0.174 g, 1 mmol) was added and the reaction mixture was stirred magnetically at room temperature for 2 h. TLC monitored the progress of the reaction (eluent; CCl_4/ Et_2O: 5/2). After completion of the reaction, distilled water (6 mL) was added and the reaction mixture was continued to stirring for 10 min. The mixture was extracted with CH_2Cl_2 (3 × 7 mL) and was then dried over anhydrous sodium sulfate. Evaporation of the solvent followed by the preparative plate chromatography of the resulting crude material over silica gel (eluent; CCl_4/Et_2O: 5/2) gives the pure liquid benzyl acetate in 95% yield (0.142 g, Table 2).

Acknowledgment. The authors gratefully acknowledge the financial support of this work by the research council of Urmia University.

References

1. Gaertner, R. *J. Org. Chem.* **1959**, *24*, 61.
2. Cavill, G. W. K.; Clezy, P. S.; Whitfield, F. B. *Tetrahedron* **1961**, *12*, 139.
3. Aft, H.; Grant, R. R.; Molyneux, R. J. *Tetrahedron* **1967**, *23*, 1963.
4. Kaplan, L. *J. Am. Chem. Soc.* **1966**, *88*, 1833, 4970.
5. Nakano, Y.; Sakaguchi, S.; Ishii, Y. *Tetrahedron Lett.* **2000**, *41*, 1565.
6. Rao, B. R.; Nambudiry, M. E. N. *Synth. Commun.* **1991**, *21*, 1721.
7. Tamami, B.; Goudarzian, N.; Kiasat, A. R. *Eur. Polym. J.* **1997**, *33*, 977.
8. Zeynizadeh, B.; Faraji, F. *Bull. Korean Chem. Soc.* **2003**, *24*, 453.
9. Zeynizadeh, B.; Zahmatkesh, K. *J. Chin. Chem. Soc.* **2003**, *50*, 267.
10. Zeynizadeh, B.; Zahmatkesh, K. *J. Chin. Chem. Soc.* **2004**, *51*, 801.
11. Zeynizadeh, B.; Zahmatkesh, K. *J. Chem. Res.* **2003**, 522.
12. Zeynizadeh, B.; Zahmatkesh, K. *J. Chin. Chem. Soc.* **2005**, *52*, 109.
13. Pouchert, C. J.; Behnke, J. *The Aldrich Library of ^{13}C and ^{1}H FT-NMR Spectra*; Aldrich Chemical Co.: Milwaukee, 1993.
14. Mahammadpoor-Baltork, I.; Aliyan, H.; Khosropour, A. R. *Tetrahedron* **2001**, *57*, 5851.
15. McKillop, A.; Ford, M. E. *Tetrahedron* **1974**, *30*, 2467.
16. Hilborn, J. W.; MacKnight, E.; Pincock, J. A.; Wedge, P. J. *J. Am. Chem. Soc.* **1994**, *116*, 3337.
17. (a) Joshi, D. K.; Gold, M. H. *Eur. J. Biochem.* **1996**, *237*, 45. (b) Pincock, J. A.; Wedge, P. J. *J. Org. Chem.* **1994**, *59*, 5587.
18. Picraux, L. B.; Smeigh, A. L.; Guo, D.; McCusker, J. K. *Inorg. Chem.* **2005**, *44*, 7846.
19. Bhushan, V.; Chakraborty, T. K.; Chandrasekaran, S. *J. Org. Chem.* **1984**, *49*, 3974.
20. Zarbin, P. H. G.; Reckziegel, A.; Plass, E.; Oliveira, A. R. M.; Simonelli, F.; Marques, F. A. *J. Braz. Chem. Soc.* **2000**, *11*, 572.
21. Ishihara, K.; Kubota, M.; Kurihara, H.; Yamamoto, H. *J. Org. Chem.* **1996**, *61*, 4560.
22. Naik, S.; Kavala, V.; Gopinath, R.; Patel, B. K. *Arkivoc* **2006**, (*i*), 119.
23. Naik, S.; Kavala, V.; Gopinath, R.; Patel, B. K. *Arkivoc* **2006**, (*xi*), 21.
24. Buckingham, J.; MacDonald, F. *Dictionary of Organic Compounds*, 6th ed.; Chapman & Hall: New York, 1995.
25. Khan, A. T.; Islam, S.; Majee, A.; Chattopadhyay, T.; Ghosh, S. *J. Mol. Cata. A* **2005**, *239*, 158.
26. Bosco, J. W. J.; Saikia, A. K. *J. Chem. Soc. Chem. Commun.* **2004**, 1116.
27. Humber, L. G. *J. Med. Chem.* **1965**, *8*, 401.
28. Orita, A.; Tanahashi, C.; Kakuda, A.; Otera, J. *Angew. Chem. Int. Ed.* **2000**, *39*, 2877.
29. Teranishi, R.; Flath, R. A.; Guadagni, D. G.; Lundin, R. E.; Mon, T. R.; Stevens, K. L. *J. Agr. Food Chem.* **1966**, *14*, 253.
30. Procopiou, P. A.; Baugh, S. P. D.; Flack, S. S.; Inglis, G. G. A. *J. Org. Chem.* **1998**, *63*, 2342.
31. Chen, C.-T.; Kuo, J.-H.; Pawar, V. D.; Munot, Y. S.; Weng, S.-S.; Ku, C.-H.; Liu, C.-Y. *J. Org. Chem.* **2005**, *70*, 1188.
32. Choi, J. H.; Choi, Y. K.; Kim, Y. H.; Park, E. S.; Kim, E. J.; Kim, M.-J.; Park, J. *J. Org. Chem.* **2004**, *69*, 1972.
33. Byers, J. *J. Org. Chem.* **1983**, *48*, 1515.