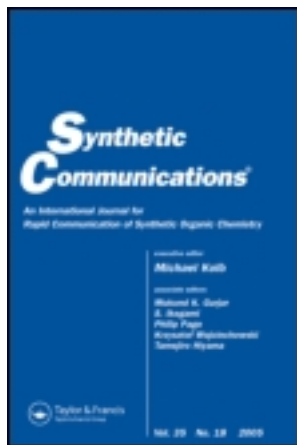


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N -Methylpyrrolidine-zinc Borohydride: As a New Stable and Efficient Reducing Agent in Organic Synthesis

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***N*-Methylpyrrolidine-zinc Borohydride: As a New Stable and Efficient Reducing Agent in Organic Synthesis**

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ABSTRACT

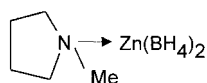
N-Methylpyrrolidine-zinc borohydride is readily prepared and used for reduction of a variety of organic compounds such as aldehydes, ketones, acid chlorides, and esters. Reactions are performed in THF at room temperature or under reflux condition and the yields are good to excellent. Complete regio-selectivity are observed in reduction of α,β -unsaturated carbonyl compounds.

Key Words: *N*-Methylpyrrolidine; Zinc borohydride; Selective reduction; α,β -unsaturated carbonyls.

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Although a large number of transition metal borohydrides are known,^[1] there are few reports on the use of these reducing agents. This is primarily because almost all of them are volatile unstable material and unless modified cannot be used in organic synthesis. Among them, zinc borohydride has been used frequently in a variety of reductive transformation.^[2] However, due to its instability it should be used as a fresh ethereal solution, even when it is supported on silica gel it should be use on the same day of its preparation.^[3] Stabilization of this worthy reducing agent has also achieved by complexation with polymeric ligands.^[4] Recently, coordination polymer of $Zn(BH_4)_2$ with bidentate ligands have been reported.^[5] But, the reducing ability of the reagent diminished severely. Herein, we introduce *N*-methylpyrrolidine-zinc borohydride [NMP- $Zn(BH_4)_2$], as a new stable reducing agent for efficient and selective reduction of aldehydes, ketones, acid chlorides, and esters. NMP- $Zn(BH_4)_2$ is a white powder which can be stored at room temperature. It decompose at $250^\circ C$ and is completely insoluble in aprotic solvents. Based on the data obtained by atomic absorption and borohydride content in iodometric titration, together with elemental analysis showed within experimental error that the reagent is in form of (I):



(I)

As shown in Table 1, a number of aldehydes are easily reduced to the corresponding alcohols with high yields in tetrahydrofuran at room temperature (Sch. 1).

Aliphatic ketones underwent complete reduction, whereas the aromatic ketones remained intact under identical condition. Reduction of aromatic ketones proceeds at longer periods in reflux condition (Table 2). Therefore, chemoselective reduction of aldehydes vs. ketones are achieved at room temperature, and the unreacted ketone is recovered in each case (Sch. 2).

Regioselective reduction of aldehydes and ketones is a clean reaction for preparation of allylic alcohols.^[6] In order to show the regioselectivity of the reagent, reduction of α,β -unsaturated aldehydes or ketones are studied. The results are summarized in Table 3. As seen, selective 1,2-reduction afforded the corresponding allylic alcohols in high yields.

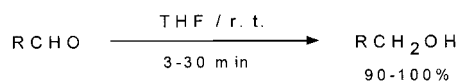
**Table 1.** Reduction of aldehydes with NMP-Zn(BH₄)₂ in THF.^a

Entry No.	R	Time (min)	Yield (%) ^b
1	C ₆ H ₅	15	92
2	2-NO ₂ C ₆ H ₄	10	98
3	4-ClC ₆ H ₄	15	97
4	2-ClC ₆ H ₄	10	100 ^c
5	2-HOC ₆ H ₄	10	100 ^c
6	3-HOC ₆ H ₄	15	100 ^c
7	4-HOC ₆ H ₄	240	100 ^c
8	4-BrC ₆ H ₄	15	89
9	4-MeC ₆ H ₄	10	92
10	MeCH=CH	10	90
11	PhCH=CH	30	98
12	<i>n</i> -C ₃ H ₇	3	96
13	<i>n</i> -C ₅ H ₁₁	6	93

^aReactions are performed at room temperature using 3:1 molar ratio of substrate to reducing agent.

^bYields refer to isolated products.

^cGC yields.

**Scheme 1.**

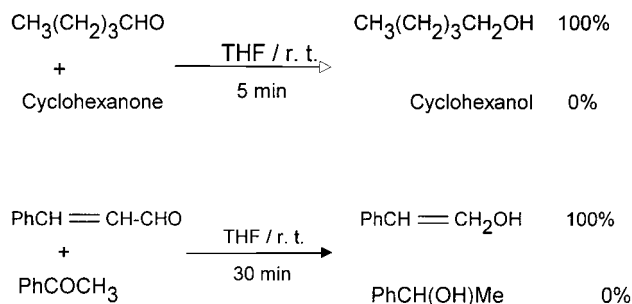
Direct conversion of acid chlorides into the corresponding alcohols is a useful reaction and some hydride reagents have been introduced for this purpose.^[7] As mentioned in Table 4, a series of acid chlorides are efficiently converted to their corresponding alcohols in good to excellent yields.

Finally, a variety of carboxylic acid esters are reduced to corresponding alcohols in moderate to good yields (Table 5). Selective reduction of aliphatic esters vs. aromatic esters has an interest in organic synthesis,^[2,8] we have found that this reagent readily induces an excellent chemo-selectivity in reduction of aliphatic esters over aromatic one as well as zinc borohydride, without any assist of sonication (Sch. 3).

It is surprising to note that almost all of the modified zinc borohydrides reagents are failed to do this transformation.

**Table 2.** Reduction of ketones (RCOR) with NMD-Zn(BH₄)₂.^a

Entry No.	R	R	Condition	Time (min)	Yield ^b (%)
1	C ₆ H ₅	CH ₃	Reflux	90	100
2	5-MeOC ₆ H ₄	CH ₃	Reflux	120	100
3	C ₆ H ₅	C ₆ H ₅	Reflux	60	95
4	4-ClC ₆ H ₄	C ₆ H ₅	Reflux	40	100
5	Ph	PhCO	Reflux	40	93 ^c
6	2-ClC ₆ H ₄	C ₆ H ₅	Reflux	30	100
7	<i>n</i> -C ₄ H ₉	CH ₃	r.t	15	95
8	CH ₃	CH ₃	r.t	5	90
9	α -Ionone		r.t	90	96
10	4-Phenylcyclohexanone		r.t	60	95
11	Cyclohexanone ^d		r.t	5	100
12	Cyclopentanone ^d		r.t	25	100

^aReactions were performed in THF using an equimolar ratio of reactants.^bYields refer to isolated products.^c1,2-Diphenyl ethylene glycol is obtained as sole product.^dGC yields.**Scheme 2.**


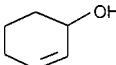
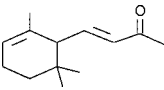
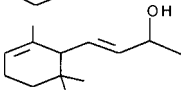
EXPERIMENTAL

Chemicals were either prepared in our laboratory or were purchased from Fluka, Merck, or BDH companies. All reaction products are known compounds and were identified by comparison of their spectra and physical data with those of the authentic samples. Reaction monitoring

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Table 3. Regioselective reduction of α,β -unsaturated aldehydes, ketones, and esters with NMD-Zn(BH₄)₂ in THF.

Entry No.	Substrate	Product	Time (min)	Yield (%) ^a
1	MeCH=CHCHO	MeCH=CHCH ₂ OH	10	90
2	PhCH=CHCHO	PhCH=CHCH ₂ OH	30	98
3	PhCH=CHCOMe	PhCH=CHCH(OH)Me	55	98
4	PhCH=CHCOPh	PhCH=CHCH(OH)Ph	70	97
3			60	95 ^b
4			90	96 ^b
5	MeCH=CHCO ₂ Me	MeCH=CHCH ₂ OH	45	90
6	PhCH=CHCO ₂ Me	PhCH=CHCH ₂ OH	65	94

^aYields refer to isolated.^bGC yields.**Table 4.** Reduction of acid chlorides (R-COCl) with NMP-Zn(BH₄)₂.^a

Entry No.	R	Time (min)	Yield (%)
1	C ₆ H ₅	120	100
2	2-ClC ₆ H ₄	70	82
3	3-NO ₂ C ₆ H ₄	40	98
4	4-NO ₂ C ₆ H ₄	35	100
5	4-ClC ₆ H ₄	70	100
6	CH ₃ (CH ₂) ₃ CH ₂	60	85
7	CH ₃ (CH ₂) ₅ CH ₂	70	89

^aReactions are conducted in THF at room temperature using 1:1 ratio of reducing agent to ester.

and purity determination of the products were accomplished by TLC. The IR and NMR spectra were recorded on Pye-unicam SP 1100 spectrophotometer and JEOL 60 MHz spectrometer, respectively. Elemental analysis were performed on a LECO 250 instrument.

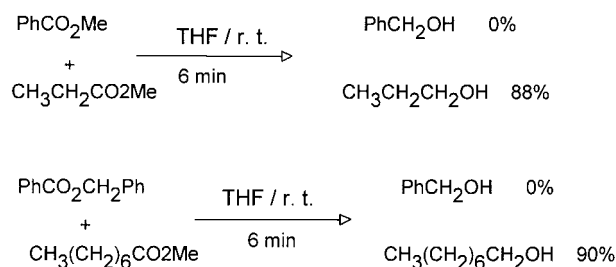
**Table 5.** Chemoselective reduction of esters with NMP-Zn(BH₄)₂.^a

Entry No.	Esters	Time (h)	Yield (%) ^b
1	PhCO ₂ Me	36	52
2	PhCO ₂ Me	0.1	0
3	PhCO ₂ CH ₂ Ph	36	60
4	PhCO ₂ CH ₂ Ph	0.1	0
5	<i>n</i> -C ₈ H ₁₇ CO ₂ Et	0.1	90
6	CH ₃ CO ₂ Et	0.1	85 ^c
7	CH ₃ CH=CHCO ₂ Et	0.75	92
8	CH ₃ CH ₂ CO ₂ Me	0.1	88 ^c

^aReactions are conducted in THF at room temperature using 1:1 ratio of reducing agent to ester.

^bYields refer to isolated.

^cGC yields.

**Scheme 3.**

Preparation of *N*-Methylpyrrolidine Zinc Borohydride [NMP-Zn(BH₄)₂]

To a freshly prepared ethereal solution of zinc borohydride (0.03 mol, 200 mL), *N*-methylpyrrolidine (2.56 g, 0.03 mol) was added in drop wise. Then, the mixture stirred at room temperature for 1.0 h under nitrogen atmosphere. The precipitate filtered off and washed with diethyl ether (10 mL). The white powder dried in vacuum desiccator to produce (4.3 g, 80% yield). Elemental analysis; found: C, 33.28; H, 19.06; N, 7.78; Zn, 36.42. Calculated: C, 33.35; H, 19.00; N, 7.76; Zn, 36.32.

**General Procedure for Reduction of Aldehydes, Ketones, and Esters with [NMP-Zn(BH₄)₂]**

To a solution of substrate (1.0 mmol) in tetrahydrofuran (10 mL), the reagent (0.06 g, 0.33 mmol) was added. The reaction mixture stirred at room temperature for specified time (Tables 1–5). Progress of the reaction is monitored by TLC. After completion of the reaction, 5% HCl (15 mL) was added and stirred for 10 min. On extraction with ether (20 mL), the organic layer was dried over Mg(SO₄)₂. Evaporation of the solvent under reduced pressure gave the desirable product.

General Procedure for the Reduction of Acylchlorides with NMP-Zn(BH₄)₂

To a tetrahydrofuran solution (10 mL) of acyl chloride (1.0 mmol) was added NMP-Zn(BH₄)₂ (0.18 g, 1.0 mmol). The mixture was then stirred at room temperature until completion of the reaction; as monitored by TLC. After addition of 5% HCl (10 mL), the mixture extracted with diethyl ether (2 × 20 mL). The combined organic layers were dried on Mg(SO₄) and evaporated to give the corresponding alcohol.

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