HETEROCYCLES, Vol. 78, No. 6, 2009, pp. 1541 - 1548. © The Japan Institute of Heterocyclic Chemistry
Received, 16th November, 2008, Accepted, 29th January, 2009, Published online, 2nd February, 2009
DOI: 10.3987/COM-08-11603

# TETRAHYDROPYRIMIDINE DERIVATIVES AS EFFICIENT ORGANIC REDUCTANTS FOR TRANSFER HYDROGENATION

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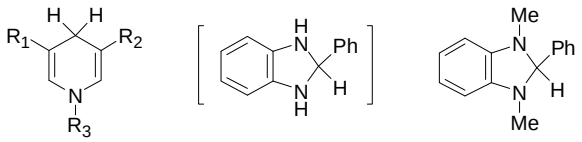
**Abstract** – Two six-membered heterocyclic organic reductants, 1-acetyl-2,3-dimethyltetrahydropyrimidine (**ADMP**) and 1-tosyl-2,3-dimethyltetrahydro-pyrimidine (**TDMP**), were designed and synthesized for transfer hydrogenation. It was shown that both the two reductants could directly reduce a variety of aldehydes and imines to the corresponding saturated products in good yields.

The investigations on heterocycles having hydrogen-donating ability as practical reductants have attracted attention in organic chemistry in recent years due to their good chemoselectivity, mild reaction condition, easily asymmetric modification as well as transition metal-free property which is especially important in medicinal area.[1-23] Because 1,4-dihydropyridines are known to be the active part of the reduced form of the nicotinamide adenine dinucleotide (**NADH**), which plays a vital role in many biological reductions,[1] 1-benzyl-1,4-dihydronicotinamide, Hantzsch 1,4-dihydropyridine, 10-methyl-9,10-dihydroacridine, and many other 1,4-dihydropyridine derivatives have been extensively used as models to mimic the function of **NADH**, and indeed showed to have excellent reducibility in some reducing reactions.[2-14] In addition to 1,4-dihydropyridine derivatives, some attention has also been paid to five-membered heterocycles, such as 2-phenylbenzimidazoline (**PBI**) and its derivative 1,3-dimethyl-2-phenylbenzimidazoline (**DMBI**).



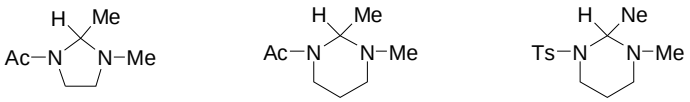

**NADH** models **PBI** **DMBI**

**Scheme 1**

Twenty years ago, Chikashita and coworkers reported that **DMBI** and **PBI** could selectively reduce C-C double bonds conjugated with strong electron-withdrawing groups (CN, $NO_2$, COMe)[15-17] to the

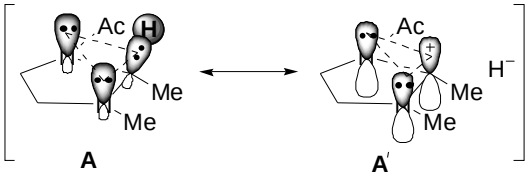
corresponding saturated compounds. Thereafter, this group reported that **DMBI** could reduce a series of α-halocarbonyl compounds to their corresponding aldehydes or ketones without affecting the carbonyl group.[18] Also, **DMBI** or its analog were used as reductant in photoinduced electron transfer (PET) reaction systems for the reduction of α,β-epoxy ketone, aromatic ketones, etc.[19-23] However, subsequent activities have been carried out to focus on the mechanistic details of these systems,[24-32] little attention has been paid in organic synthesis.

Recently, we developed a mild, efficient, and selective five-membered heterocyclic organic reductant, 1-acetyl-2,3-dimethylimidazolidine (**ADMI**), for the reduction of aromatic, aliphatic and α,β-unsaturated aldehydes as well as imines in good yields.[33] In the present work, we wish to report two six-membered heterocyclic organic reductants, 1-acetyl-2,3-dimethyltetrahydropyrimidine (**ADMP**) and 1-tosyl-2,3-dimethyltetrahydropyrimidine (**TDMP**), and these successful applications in transfer hydrogenation reaction.



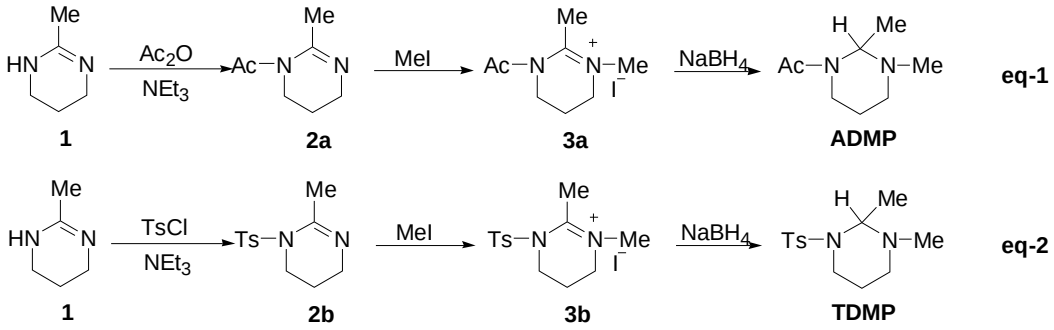

**Scheme 2**

Recently, we described **ADMI** as a five-membered heterocyclic compound showing excellent reactivity for reducing a series of aldehydes and imines.[33] The deuterated experiment demonstrated that the reduction involving the transfer of a hydrogen atom to substrates from C-2 position of **ADMI**. A plausible mechanism is that the 1,3-diaza-type structure in **ADMI** possibly allows a hyperconjugative interaction between nonbonding tertiary amine lone pair and the $\sigma^*$ (C2-H) orbital (expressed by resonance between the canonical structure **A**-**A′**, Scheme 3), thus, induces a weakening of the C2-H bond and an increase of negative charge density at the hydrogen atom.[32] In fact, similar structural feature is also found in the structure of **PBI**, **DMBI** as well as a 1,3,2-diazaphospholene compound.[34] Although the detailed mechanism is unclear at present, the results have prompted us to exploit new 1,3-diaza-type heterocycles, such as six-membered heterocycles **ADMP** and **TDMP**, for their application in organic synthesis.




**Scheme 3**

**ADMP** could be readily prepared in a three-step procedure (eq-1) involving (i) acetylation of the starting material, 2-methyl tetrahydropyrimidine (**1**), with $Ac_2O$ to **2**, and (ii) methylation of **2** with $CH_3I$ to **3** and (iii) subsequent reduction with $NaBH_4$ to the objective compound. **TDMP** was synthesized by the same procedure except that TsCl was used in the first step (eq-2).



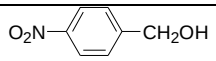
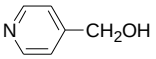
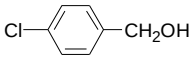
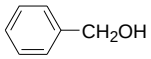
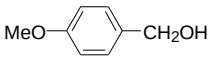
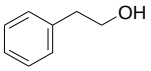
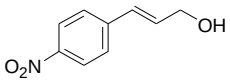
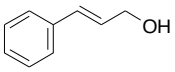
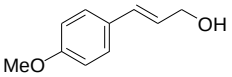

Subsequently, the potential reduction ability of **ADMP** and **TDMP** was tried with 4-nitrobenzaldehyde as substrate in our standard conditions (reductant: 1 mmol, substrate: 1 mmol, $Mg(ClO_4)_2$: 0.1 mmol, MeCN-MeOH: 1:1, 4 mL).[33] As expected, both the two reductants showed good reactivity at room temperature. The reactions could be completed within 12 hr and 4-nitrobenzyl alcohol was obtained in 85% and 83% yields for **ADMP** and **TDMP**, respectively. It is interesting to note that when the temperature was raised to 50 $^oC$, the reactions could be completed after 0.5 hr with the improved yields of 90% and 92% for **ADMP** and **TDMP**, respectively. The results suggest that the reaction rate of this type of reductive reaction is sensitive to temperature, and **ADMP** and **TDMP** have similar reactivity in the condition.

Next, we examined the application scope with **ADMP** as reductant and various aldehydes as substrates, as shown Table 1. It was found that all aldehydes tested in this study, including electron-deficient, electron-rich, and aliphatic aldehydes could be efficiently reduced in good yields within 1 hr (Entry 1-6). Noteworthy is that the α, β-unsaturated aldehydes examined can be reduced to the corresponding unsaturated alcohols in high yields without any effect on the carbon-carbon double bonds (Entry 7-9), and the desired unsaturated alcohols were obtained as the sole products. The scope of this new reduction was further extended to a variety of imines. As shown in Table 2, for both *N*-tosyl imines and N-phenyl imines, the reductions worked well in our conditions. The low yield for *N*-tosyl-4-nitrobenzaldimine (Entry 1) and *N*-phenyl-4-nitrobenzaldimines (Entry 4) is mainly due to their quick decomposition in reaction conditions. In addition, similar case could also be found when **TDMP** as reductant. However, no effort was made to separate these reducing products, and only TLC was used to evaluate its reactivity toward various substrates.

In summary, we have developed two efficient six-membered heterocyclic organic reductants, 1-acetyl-2,3-dimethylpyrimidine (**ADMP**) and 1-Ts-2,3-dimethylpyrimidine (**TDMP**), for the reduction

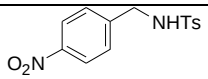
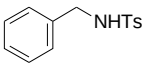
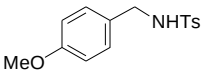
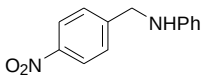
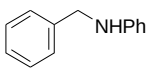
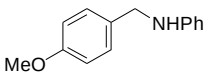
of aromatic, aliphatic and α,β-unsaturated aldehydes as well as imines in good yields. Investigation to understand the reducing mechanism and to evaluate the process with a broader scope of substrates are in progress in our lab.

**Table 1** Transfer hydrogenation of **ADMP** with various aldehydes[a]

| Entry | Products | Time (h) | Yield (%)[b] |
|---|---|---|---|
| 1 |  | 0.5 | 90 |
| 2 |  | 0.5 | 84 |
| 3 |  | 0.5 | 87 |
| 4 |  | 1 | 93 |
| 5 |  | 1 | 88 |
| 6 |  | 1 | 90 |
| 7 |  | 1 | 93 |
| 8 |  | 1 | 94 |
| 9 |  | 1 | 95 |

[a]Conditions: **ADMP** (1.0 mmol), substrate (1.0 mmol), $Mg(ClO_4)_2$ (0.1 mmol), MeCN-MeOH: 1:1 (v/v), 4 mL, 50 °C. [b] Isolated yields.

**Table 2** Transfer hydrogenation of **ADMP** with various imines[a]

| Entry | Products | Time (h) | Yield (%)[b] |
|---|---|---|---|
| 1 |  | 2 | 60 |
| 2 |  | 0.5 | 94 |
| 3 |  | 2 | 95 |
| 4 |  | 5 | 32 |
| 5 |  | 3 | 80 |
| 6 |  | 3 | 75 |

[a]Conditions: **ADMP** (1.0 mmol), substrate (1.0 mmol), $Mg(ClO_4)_2$ (0.1 mmol), MeCN-MeOH: 1:1 (v/v), 4 mL, 50 °C. [b] Isolated yields.

## EXPERIMENTAL

Commercially available compounds were used without further purification. Solvents were dried according to standard procedures. All reactions were magnetically stirred and monitored by thin-layer chromatography (TLC) using Huanghai $GF_{254}$ silica gel coated plates. Flash chromatography (FC) was carried out using silica gel 60 (230-400 mesh). The $^1$H NMR and $^{13}$C NMR spectra were recorded at 300 and 75MHz, respectively. The following abbreviations were used to explain the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; br = broad. MS spectra were obtained on a JMS-D300 GC/MS spectrometer. IR spectra were obtained on a Shimadzu IR-1700 spectrophotometer. Melting points were uncorrected.

### Synthesis of 1-acetyl-2,3-dimethyltetrahydropyrimidine (ADMP)

2-Methyltetrahydropyrimidine (0.98 g, 10 mmol) was dissolved in 15 mL dry $CH_2Cl_2$ at 0 $^oC$, followed by the addition of triethylamine (1.01 g, 10 mmol). Then this solution was added dropwise a solution of acetic anhydride (1.02 g, 10 mmol) in 5 mL $CH_2Cl_2$. After the addition, the reaction mixture was allowed to rt for an additional 3 h. The resulted solution was treated with 10% aqueous $NaHCO_3$ (10 mL). After stirring 0.5 h, the mixture was extracted with $CH_2Cl_2$, and the organic layers were washed with the saturated brine, and dried over anhydrous sodium sulfate. Evaporation of $CH_2Cl_2$ in vacuo gave 0.96 g of 1-acetyl-2-methyltetrahydropyrimidine (**2a**) as an oil (yield: 69%).

1-Acetyl-2-methyltetrahydropyrimidine (0.96 g, 6.9 mmol) and iodomethane (1.3 mL, 20.7 mmol) were stirred in a sealed flask for 5 h in rt. Then 2 mL of acetone was added, the mixture was stirred for a few minutes, and the solid obtained was collected by vacuum filtration to give 1.36 g of 1-acetyl-2,3-dimethyltetrahydropyrimidinium iodide (**3a**) as a white solid (yield: 70%). $^1$H NMR (300 MHz, δ ppm, $CDCl_3$): 2.38 (m, 2H), 2.54 (s, 3H), 2.75 (s, 3H), 3.50 (s, 3H), 3.86 (m, 2H), 4.14 (t, $J$ = 5.70, 2H).

1-Acetyl-2,3-dimethyltetrahydropyrimidinium iodide (0.85 g, 3 mmol) was dissolved in 10 mL of MeCN at 0 $^oC$, followed by the addition of $NaBH_4$ (0.13 g, 3.3 mmol). After the addition, the reaction mixture was allowed to rt for an additional 5 h. The resulted solution was treated with 50 mL of water. The mixture was extracted with $CH_2Cl_2$, and the organic layers were washed with the saturated brine, and dried over anhydrous sodium sulfate. Evaporation of dichloromethane in vacuo gave 0.43 g of 1-Acetyl-2,3-dimethyltetrahydropyrimidine (**ADMP**) as a clear oil (yield: 91%). $^1$H NMR (300 MHz, δ ppm, $D_2O$): 1.29–1.44 (2×m, 5H), 1.82–1.92 (2×s, 3H), 2.36–2.45 (2×s, 3H), 2.65 and 3.58 (2×m, 2H), 3.21 and 4.14 (2×m, 2H), 4.53 and 5.01 (2×m, 1H). IR (film) cm$^{-1}$: 2960, 2381, 1635, 1427, 1369, 1296, 1072. MS m/z: 157 ($[M+1]^+$). Anal. Calcd for $C_8H_{16}N_2O$: C, 61.50; H, 10.32; N, 17.93. Found C, 61.34; H, 10.21, N, 17.85.

### Synthesis of 1-tosyl-2,3-dimethyltetrahydropyrimidine (TDMP)

2-Methyltetrahydropyrimidine (0.98 g, 10 mmol) was dissolved in 15 mL dry $CH_2Cl_2$ at 0 $^oC$, followed by the addition of triethylamine (1.01 g, 10 mmol). Then this solution was added dropwise a solution of TsCl (1.905 g, 10 mmol) in 10 mL $CH_2Cl_2$. After the addition, the reaction mixture was allowed to rt for an additional 3 h. The resulted solution was treated with 10% $NaHCO_3$ (10 mL). After stirring 0.5 h, the mixture was extracted with $CH_2Cl_2$, and the organic layers were washed with the saturated brine, and dried over anhydrous sodium sulfate. Evaporation of $CH_2Cl_2$ in vacuo gave 1.27 g of 1-tosyl-2-methyltetrahydropyrimidine (**2b**) as an oil (yield: 50%).

1-Tosyl-2-methytetrahydropyrimidine (1.27 g, 5 mmol) and iodomethane (0.94 mL, 15 mmol) were refluxed in $Et_2O$ (10 mL) for 8 h. After cooled to rt, 1 mL of acetone was added. The mixture was stirred for several minutes, and the solid obtained was collected by vacuum filtration to give 1.38 g of 1-tosyl-2,3-dimethyltetrahydropyrimidinium iodide (**3b**) as a white solid (yield: 70%). $^1H$ NMR (300 MHz, δ ppm, $CDCl_3$): 2.33 (m, 2H), 2.44 (s, 3H), 2.71 (s, 3H), 3.45 (s, 3H), 3.85 (m, 2H), 4.30 (m, 2H), 7.44 (d, *J* = 7.89, 2H), 7.91 (d, *J* = 7.92, 2H).

1-Tosyl-2,3-dimethyltetrahydropyrimidinium iodide (1.18 g, 3 mmol) was dissolved in 10 mL of MeCN at 0 $^oC$, followed by the addition of $NaBH_4$ (0.13 g, 3.3 mmol). After the addition, the reaction mixture was allowed to rt for an additional 5 h. The resulted solution was treated with 50 mL of water. The mixture was extracted with $CH_2Cl_2$, and the organic layers were washed with the saturated brine, and dried over anhydrous sodium sulfate. Evaporation of $CH_2Cl_2$ in vacuo gave 0.76 g of 1-tosyl-2,3-dimethyltetrahydropyrimidine (**TDMP**) as a clear oil (yield: 95%). $^1H$ NMR (300 MHz, δ ppm, $CDCl_3$): 1.33 (d, *J* = 6.54, 3H), 1.54 (m, 1H), 2.05 (m, 1H), 2.40 (s, 3H), 2.77 (s, 3H), 2.83 (m, 1H), 2.96 (t, *J* = 12.96, 1H), 3.24 (t, *J* = 12.69, 1H), 3.75 (m, 1H), 4.74 (m, 1H), 7.28 (d, *J* = 7.74, 2H), 7.60 (d, *J* = 7.86, 2H). IR (film) $cm^{-1}$: 2956, 2380, 1596, 1450, 1384, 1338, 1157. MS m/z: 269 ($[M+1]^+$). Anal. Calcd for $C_{13}H_{20}N_2O_2S$: C, 58.18; H, 7.51; N, 10.44. Found C, 58.24; H, 7.25, N, 10.25.

**General procedure for the transfer hydrogenation reaction with ADMP and TDMP as reductants**

To a solution of substrate (1 mmol) and $Mg(ClO_4)_2$ (22.3 mg, 0.1 mmol) in MeOH (2 mL) was added a solution of reductant (1 mmol) in 2 mL of anhydrous MeCN. The reaction mixture was stirred at 50 $^oC$ and monitored by TLC. Upon completion, the solvent was removed in vacuo and the residue was chromatographed on silica gel to give the desired products.

## ACKNOWLEDGEMENTS

We thank the National Natural Science Foundation of China (No. 20502014 and 20772073) for financial support.

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