REACTIVITY OF RIEKE MANGANESE: SYNTHESIS OF PYRROLIDINE AND PIPERIDINE DERIVATIVES[1†]

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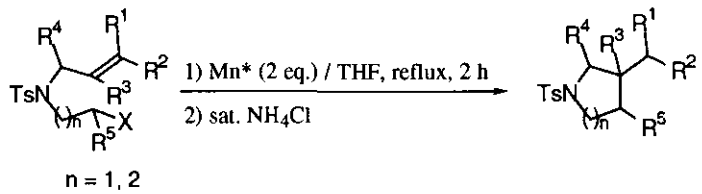
Abstract - Low-valent manganese generated by the reduction of manganese(II) chloride using lithium naphthalenide (Rieke manganese) promotes reactions of alkyl halides with electrophiles such as acyl chloride, aldehyde, and ketone to afford alkylation products. *N*-Haloalkyl-*N*-allyltosylamides are converted to pyrrolidine and piperidine derivatives in high yields. In the reactions of aromatic aldehyde and ketone, pinacol-type coupling products are produced.

Organomanganese reagents are known to be chemoselective toward carbonyl functionalities in the alkylation.[2] Such chemoselectivity is expected to be applied for the generation and reactions of organomanganese reagents bearing functional groups in their molecules such as the well-known zinc reagents.[3] In this context, we tried to generate the organomanganese species[4] by the reduction of halogenated compounds using low-valent manganese that was prepared by reduction of manganese(II) chloride using lithium naphthalenide as a reductant (Rieke manganese).[5] Contrary to our expectations, we found a new reaction for the synthesis of nitrogen heterocycles (Scheme 1). We also wish to report some other reactions as well as the cyclization process.

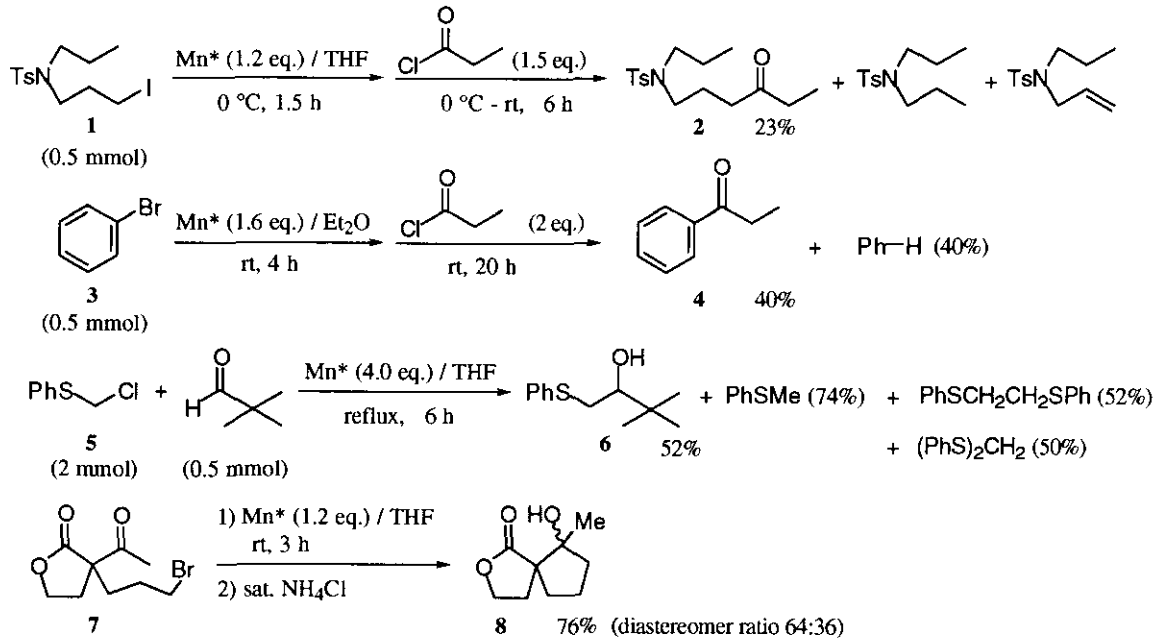
Scheme 1



First, we examined the generation and reactions of organomanganese reagents from several halides bearing a hetero-functionality with electrophiles. When iodopropyltosylamide (**1**) was treated with Rieke manganese, the corresponding manganese reagent seemed to be generated to some extent, and upon the addition of an acid chloride, the acylated product (**2**) was obtained in modest yield along with *N*,*N*-dipropyltosylamide and *N*-allyl-*N*-propyltosylamide (Scheme 2).[6] A phenylmanganese reagent was also produced in ether,[7] while in THF propiophenone was not detected in the reaction mixture. These results

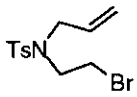
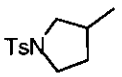
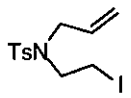
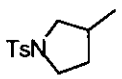
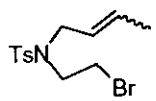
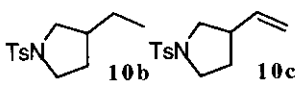
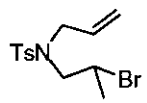
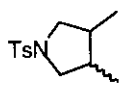
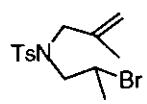
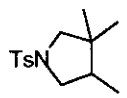
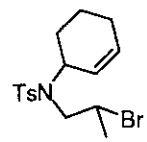
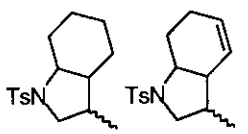
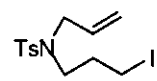
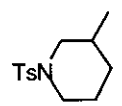
imply participation of an intermediate that behaves like a radical species in the reactions.[8] Thiomethylation of aldehyde was also achieved when a mixture of chloromethyl sulfide (**5**) and an aldehyde was treated with Rieke manganese.[9] Moreover, halo ketone (**7**) efficiently cyclized to yield spirolactone (**8**). Such a one-step procedure is superior to the stepwise procedure in the addition of an alkyl group toward a carbonyl group, and these "Barbier-type" conditions are particularly effective in the intramolecular reaction.

Scheme 2



Another cyclization reaction was also found when halo olefins were employed as a substrate (Scheme 1, Table 1). As can be seen in Table 1, starting from primary halides, the yields of products were generally lower than those from secondary halides, and an appreciable amount of *N*-allyltosylamide was produced as a byproduct.[10] Such a difference in reactivity is possibly due to the strong radical character of the secondary manganese species or the difficulty of the second one-electron reduction of the transient radical produced by the first one-electron reduction of the secondary halide. Deuterium was not incorporated into products after quenching the reaction with DCl / D_2O. Termination of the reaction may be due to abstraction of the hydrogen atom from the solvent or disproportionation of the radical and/or β-elimination of hydridomanganese. A representative procedure for the cyclization of halo olefin is as follows. Manganese(II) chloride (1.0 mmol) was placed in a 10-mL two-necked, round-bottom flask with a three-way stopcock and a septum. The apparatus was dried by heating under reduced pressure and purged with argon. To this flask naphthalene (2.2 mmol) and lithium (2.0 mmol) were introduced under flushing argon atmosphere, and THF (1.5 mL) was added. The mixture was stirred at room temperature for 3 h. The resultant dark-brown mixture was refluxed and a solution of *N*-2-bromoethyl-*N*-allyltosylamide (**9a**) (0.5 mmol) in THF (0.5 mL) was added. The reflux was continued for 2 h. The mixture was cooled and poured into a saturated NH_4Cl solution. After extraction with ether, drying over Na_2SO_4, filtration and evaporation, a crude mixture was obtained. This mixture was subjected to column chromatography on silica gel (hexane / ethyl acetate = 10 / 1, R_f = 0.16) to afford a pure product (**10a**) (72 mg, 0.3 mmol, 60%).

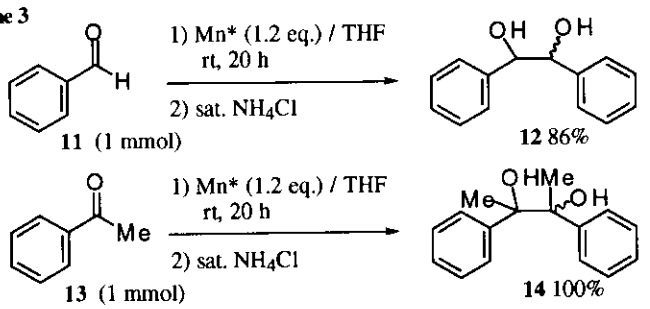
Table 1. Cyclization of Halo Olefin (9) Using Rieke Manganese[a]

Entry	Substrate (9)	Products (10)	Yield%[b]
1	 **9a**	 **10a**	60
2	 **9b**	 **10a**	60
3	 **9c**	 **10b** **10c** (79 : 21)[c]	44
4	 **9d**	 **10d**	90[d]
5	 **9e**	 **10e**	85
6	 **9f**	 **10f** **10g** (73 : 27)[c]	80
7[e]	 **9g**	 **10h**	34

[a]Reaction conditions: A solution of *N*-haloalkyl-*N*-*p*-toluenesulfonamide (**9**) (0.5 mmol) in THF (0.5 mL) was added to Rieke manganese (1.0 mmol) in THF (1.5 mL) at reflux under argon atmosphere and the reaction mixture was stirred for 2 h at the same temperature. [b]Isolated yield by column chromatography on silica gel. [c]Determined by ^{1}H NMR integration. [d]The isomer ratio was determined as 2 : 1. [e]0.6 mmol of Rieke manganese was used.

Rieke manganese reacts with aromatic aldehyde (**11**) and ketone (**13**) to afford homocoupled diol (**12**) and (**14**), respectively in high yield (Scheme 3).

Scheme 3



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REFERENCES AND NOTES

†The paper is dedicated to the celebration of the 80th birthday of Professor Dr. Bernhard Witkop.

1. A part of this study was presented in the 67th annual meeting of the Chemical Society of Japan, 1994, Tokyo, 2K1 36; abstract II-p.1092.

2. G. Cahiez, 'Encyclopedia of Reagents for Organic Synthesis,' ed. by L. Paquette, Wiley, Chichester, 1995, pp. 925-928.

3. For reviews, see P. Knochel, *Synlett*, 1995, 393; P. Knochel and R. D. Singer, *Chem. Rev.*, 1993, **93**, 2117.

4. M. Hojo, H. Harada, H. Ito, and A. Hosomi, *J. Am. Chem. Soc.*, 1997, **119**, 5459; M. Hojo, H. Harada, H. Ito, and A. Hosomi, *Chem. Commun.*, 1997, 2077.

5. S. -H. Kim, M. V. Hanson, and R. D. Rieke, *Tetrahedron Lett.*, 1996, **37**, 2197.

6. Although the amounts of these byproducts actually produced in this stepwise acylation were not analyzed, the reduction of iodide (**1**) with Rieke manganese without the consecutive addition of propionyl chloride afforded 93% of *N,N*-dipropyltosylamide and 7% of *N*-allyl-*N*-propyltosylamide.

7. In a crude reaction mixture obtained by the reaction in ether, benzene (about 40%) and bromobenzene (about 10%) were detected by GC and GCMS.

8. K. Takai, T. Ueda, N. Ikeda, and T. Moriwake, *J. Org. Chem.*, 1996, **61**, 7990.

9. Based on pivalaldehyde (0.5 mmol), 74% of thioanisol (0.37 mmol), 52% of 1,2-bis(phenylthio)ethane (0.26 mmol) and 50 % of bis(phenylthio)methane (0.25 mmol) were produced as byproducts.

10. *N*-Allyltosylamide may be produced through β-elimination from an anionic intermediate.

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