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LETTERS

A New Convenient Procedure to Prepare Organomanganese Reagents from Organic Halides and Activated Manganese

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Abstract: A new method to obtain activated manganese metal, especially attractive for large scale preparative organic chemistry, is described. The key point is the use of 2-phenylpyridine as electron carrier to reduce manganese chloride by lithium. The active manganese thus obtained was used to prepare various organomanganese reagents from organic halides. The reactivity of these reagents has been studied (acylation, 1,2- or 1,4-addition, alkylation and alkenylation).

Organomanganese reagents prove to be very useful in organic chemistry and they are especially interesting for their high chemoselectivity.[1] In theory, it is possible to prepare various functionalized organomanganese reagents Unfortunately, it is not possible to obtain them classically by transmetallation from manganese halides and organolithium or magnesium reagents since these ones are too reactive to tolerate many functional groups. These considerations have prompted us and others to try to prepare organomanganese reagents, like Grignard reagents, directly from activated or non-activated manganese metal and organic halides.

Thus, we have previously shown that manganese-mediated Barbier and Reformatsky reactions can be performed by using commercial manganese metal alone or in the presence of a catalytic amount of metallic salts (ZnX_2, CuX_2...).[2] Two other groups have reported that treatment of manganese by $TMSCl/PbCl_2$[3] or in a less extend by iodine[4] also allows to obtain similar results. However, these procedures are only convenient for reactive organic halides (allylic halides, α-halogenoesters...), with the less reactive ones, *i.e.* alkyl halides, activated manganese metal (Mn*) is required.[5] This latter can be obtained by reducing a manganese halide with lithium aluminium hydride[6] or more efficiently with potassium/graphite[7] according to the elegant method reported by Fürstner. However, until now, the simplest route is the reduction with lithium in the presence of naphthalene as electron carrier.[8]

It should be emphasized that with this procedure, it is necessary to destroy the excess of activated manganese with 1,2-dibromoethane before adding the electrophile and the final product is always obtained as a mixture with a large amount of naphthalene (generally 1 to 2 equiv.), which is very difficult to eliminate. Moreover, the scope of the synthetic applications seems limited since almost all the reported examples involve the acylation with aromatic carboxylic acid chlorides or the Pd or Ni-catalyzed aryl-aryl coupling reaction.[8]

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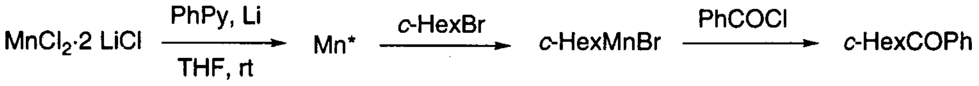
In order to avoid these drawbacks, we propose to replace naphthalene by a new electron carrier, the 2-phenylpyridine that is very easily eliminated during the final work-up by acid washing. In addition, as shown below, the organomanganese reagents prepared from the Mn* thus obtained can be used to perform all the reactions previously described with their counterparts obtained by transmetallation.

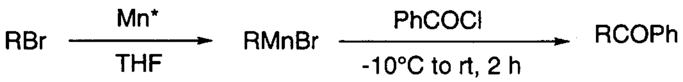
Our first experiment was achieved from Mn* prepared by reduction of a THF solution of the ate complex $MnCl_2{\bullet}2LiCl$[1b] by lithium in the presence of 0.3 equivalent of 2-phenylpyridine (PhPy) at room temperature. After one hour, a black Mn* slurry was obtained. Cyclohexyl bromide was then added at 0°C, and the reaction mixture was stirred for 3h at 5°C. Quenching with benzoyl chloride gave cyclohexylphenylketone in 91% yield.



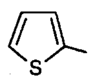
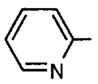
$$MnCl_2{\cdot}2\,LiCl \xrightarrow[\text{THF, rt}]{\text{PhPy, Li}} Mn^* \xrightarrow{c\text{-HexBr}} c\text{-HexMnBr} \xrightarrow{\text{PhCOCl}} c\text{-HexCOPh}$$

We have then applied this procedure to various organic halides (Table I). Our attempts with *n*, s-alkyl and aryl bromide as well as benzyl chloride were successful. However, according to the nature of the organic halide, it is necessary to vary the temperature and the reaction time (5°C to rt and 3h to 12h, see table I)

Table I : Preparation of Organomanganese Reagents from Activated Manganese



$$RBr \xrightarrow[\text{THF}]{Mn^*} RMnBr \xrightarrow[-10°C \text{ to rt, 2 h}]{\text{PhCOCl}} RCOPh$$

R	Reaction Conditions (insertion of Mn°)	Yield (%)[a]
n-Hept	5°C, 3h	93
c-Hex	5°C, 3h	91
s-Bu	5°C, 3h	73
	rt, 12h	80
	rt, 12h	56
m-Chlorophenyl	rt, 12h	72
$PhCH_2$[b]	5°C, 3h	72

a/Yield of isolated product. b/ The reaction was performed from $PhCH_2Cl$

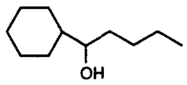
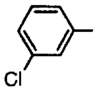
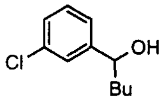
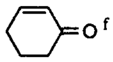
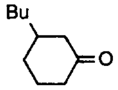
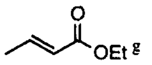
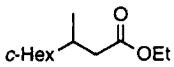
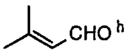
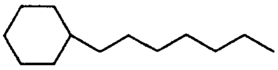
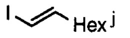
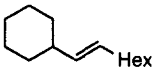
Organomanganese reagents thus prepared have a wide scope of applications in organic synthesis (Table II). Indeed, acylation with aromatic but also aliphatic carboxylic acid chlorides provides the corresponding ketones in good yields. It is worthy of note that with aliphatic acid chlorides the reaction must be performed in the presence of a catalytic amount of copper chloride.

The 1,2-addition to aldehydes gave good results but, surprisingly, it also requires a copper catalysis except with the very reactive benzylmanganese chloride. It is the first time that such an effect is observed with organomanganese compounds.[1]

On the other hand Cu-catalyzed 1,4-addition to conjugated enones, enals and enoates and alkylation as well as Fe-catalyzed alkenylation have been achieved in high yields.[1]

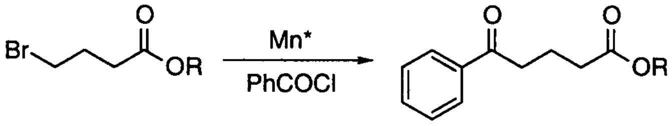
Table II : Reactivity of the Organomanganese Reagents Prepared from Activated Manganese

$$\mathrm{RBr} \xrightarrow{\mathrm{Mn}^*} \mathrm{RMnBr} \xrightarrow{\mathrm{E}} \mathrm{R\text{-}E}$$

R	Electrophile	Product	Yield (%) [a]
Hept	BuCOCl [b]	HeptCOBu	81
$PhCH_2$ [c]	BuCHO [d]	$PhCH_2CH(OH)Bu$	87
c-Hex	BuCHO [e]		77
	BuCHO [e]		72
Bu	 [f]		78
c-Hex	 [g]		89
Hept	 [h]		78
Bu	HeptI [i]	Undecane	69
c-Hex	HeptBr [i]		72
c-Hex	 [j]		79

a/ Yield of isolated product. For a typical procedure see note 9. b/ 3% CuCl, -10°C to rt, 2h. c/ $PhCH_2MnCl$ prepared from $PhCH_2Cl$. d/ -20°C, 2h. e/ 3% CuCl, -10°C, 2h. f/ 3% CuCl, 0°C, 2h. g/ 1.1eq TMSCl, 3% CuCl, 0°C, 2h. h/ 3% CuCl, -30°C, 2h. i/ 4eq NMP, 3% CuCl•2LiCl, 0°C to rt, 2h. j/ 4eq NMP, 3% $Fe(acac)_3$, rt, 2h.

In conclusion, we have reported a general method to prepare various organomanganese reagents from organic halides and activated manganese metal. The use of 2-phenylpyridine (0.3 equiv.) as electron carrier allows the preparation of manganese compounds in a large scale, moreover, it can be easily eliminated by acid washing during the final work up and eventually recycled. Of course the most interesting synthetic potential of this new method is the preparation of functionalized organomanganese reagents. As an illustration, we describe above the first preparations of alkylmanganese bromides bearing an ester group from manganese metal.



R = *s*-butyl : 66%

menthyl : 69%

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References and Notes

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9. **Typical Procedure : Preparation of 5-Dodecanone.** Freshly distilled THF (20 mL), Li (0.18 g, 26 mmol) and 2-phenylpyridine (0.62 g, 4 mmol) were introduced in a 100 mL flask under an argon atmosphere and were stirred for 1 h. In a separated 50 mL flask was prepared a solution of the ate complex $MnCl_4Li_2$ by stirring a suspension of anhydrous $MnCl_2$ (1.63 g, 13 mmol) and LiCl (1.1 g, 26 mmol) in THF (20 mL) for 30 min. Then, this yellow solution was slowly added (1 h) at room temperature with a syringe to the 2-phenylpyridine lithium solution previously prepared. Heptyl bromide (1.79 g, 10 mmol) was then added at 0°C and the resulting solution was stirred at 5°C for 3 h. Acylation was carried out by adding CuCl (0.05 g, 0.5 mmol) and valeroyl chloride (0.6 g, 5 mmol) at -10°C. The reaction mixture was stirred at rt for 2 h then quenched by HCl 3M (25 mL). The product was extracted with ether and organic layer was washed with a saturated $NaHCO_3$ solution and a saturated brine solution. After drying over $MgSO_4$, filtration and evaporation under vacuo, the product is purified by column chromatography on silica gel (cyclohexane/ethyl acetate 98:2) to give 0.5 g (81%) of 5-dodecanone.