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Preparation and Reactivity of Functionalized Aryl and Alkenylmanganese Halides[1]

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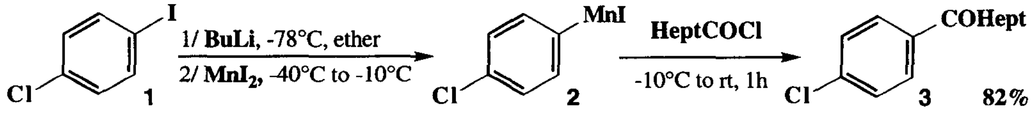
Abstract: Various functionalized aryl and alkenyl manganese halides have been prepared from the corresponding aryl and alkenylhalides according to a one-pot procedure: lithium-halogen exchange at low temperature then Li-Mn transmetallation.

Organomanganese reagents are very interesting for preparative organic chemistry since they can be used to perform, under mild conditions (very often between 0°C and rt), various useful synthetic reactions in high yields (1,2 and 1,4 additions, acylation, alkylation, alkenylation...) without involving any toxic or expensive metal or additive.[2] In addition, they are especially attractive for the elaboration of polyfunctionalyzed molecules owing to their high chemoselectivity (*i.e.* selective conversion of keto-aldehydes to ketols, of ketocarboxylic acid chlorides to diketones, of unsymmetrical diketones to ketols, selective substitution of ω-halogenoketones or ω-ketoalkenylhalides...).[2, 3] To enlarge the scope of application of the organomanganese chemistry to the synthesis of complex molecules, it was interesting to be able to prepare functionalized organomanganese compounds to introduce functionalities from both substrate and reagent. The utility of such an approach has been well demonstrated with organozinc compounds.[4] In this letter we describe our first results concerning the preparation of functionalyzed aryl and akenyl manganese compounds.

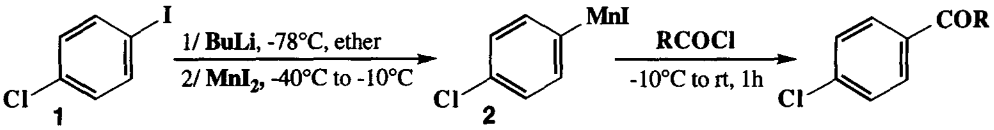
By considering the results previously described, the preparation of functionalized organomanganese compounds seemed possible since in ether or in THF various functional groups do not react with organomanganese halides RMnX. For instance, the acylation reaction generally performed in ether or THF has been successfully performed in the presence of ethyl acetate or methylene chloride as cosolvents.[2a, c] In fact, the only difficulty was to prepare the functionalized organolithium or magnesium precursors and to convert them to organomanganese halides by transmetallation without side reaction in spite of their reactivity. We have turned our attention to functionalized aryl or alkenyllithium reagents easily prepared by halogen-lithium exchange at low temperature.[5] Our first attempt was performed with *p*-chloroiodobenzene **1**.

Scheme 1



It was treated with BuLi at -78°C in ether for 15 min., then MnI_2 (1.1 equiv.) was added as an ethereal suspension[6] to the resulting *p*-chlorophenyllithium solution and the reaction mixture was progressively warmed up to -10°C before quenching with heptanoyl chloride to characterize the expected *p*-chlorophenylmanganese iodide. Under these conditions, the ketone **3** was obtained along with *p*-chlorobutyl benzene in a ratio 6:1. This product is formed during the lithium-manganese transmetallation by reaction of the intermediate aryllithium with the butyl iodide resulting from the iodine-lithium exchange. This result was unexpected since it has been shown that organomanganese halides can be prepared in the presence of butyl iodide or bromide.[7] In fact, at -78°C MnI_2 completely precipitates[6] and then dissolves again in the reaction mixture only very slowly during the warm up. Another attempt performed by replacing MnI_2 by the ate complex $MnBr_2{\bullet}2LiBr$ in solution in ether[2a] led to a poorer result (ketone **3**:alkylation product= 3:1). The proportion of *p*-chlorobutyl benzene was finally lowered by adding an ethereal suspension of MnI_2[6] at -40°C instead of -78°C (Scheme 1). Under these conditions the ketone **3** was finally obtained in 82% yield from **1** (ketone **3**:alkylation product= 19:1). The preparation of various functionalized ketones (entries 1 to 4) or ester (entry 5) from p-chlorophenylmanganese iodide**2** was reported in Table 1.

Table 1. Preparation of Polyfunctionalized Ketones or Esters by Acylation of p-Chlorophenylmanganese Iodide **2**.

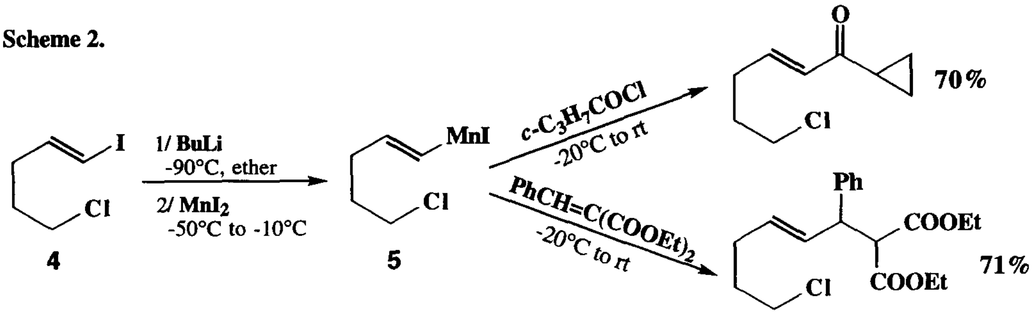


Entry	1	2	3	4	5
R	$Cl(CH_2)_3$	$Cl(CH_2)_5$	$Br(CH_2)_{10}$	c-C_3H_7	EtO
Yield (%)[a]	76	78	82	79	74

a/ Yield of isolated product.

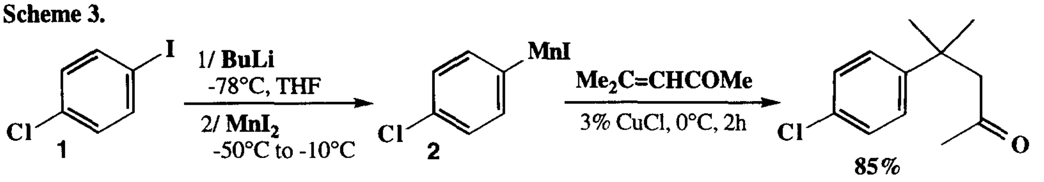
The procedure described above can also be applied to the preparation of functionalized alkenylmanganese reagents. Thus, 5-chloropentenylmanganese iodide **5** was prepared from 5-chloropentenyl iodide **4** then acylated with cyclopropylcarboxylic acid chloride in 70% yield or added to diethylbenzylidenemalonate to give 71% of the 1,4 addition product (Scheme 2).

Scheme 2.



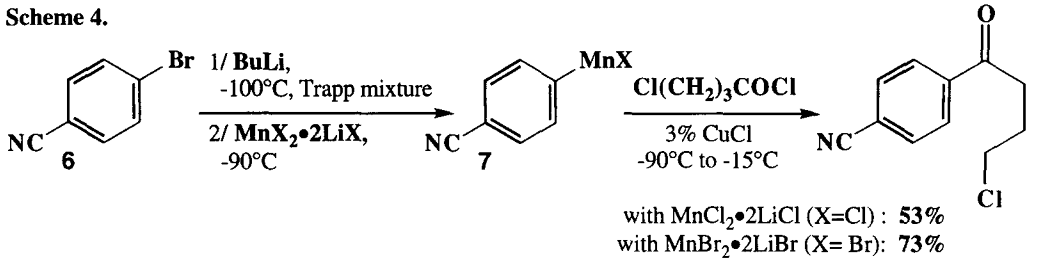
p-Chlorophenylmanganese iodide **2** can also be prepared in THF (Scheme 3) then reacted with mesityl oxide in the presence of copper salts to afford the conjugate addition product in 85% yield.

Scheme 3.



Unfortunately, with aryl or alkenyl halides bearing a functional group more reactive than a chlorine atom (*i. e.* COOR or CN), the procedure described above did not lead to the expected product or only in very low yields. Thus, from *p*-iodobenzonitrile or from esters of *p*-iodobenzoic acid the corresponding aryllithiums must be prepared then transmetalled between -100°C and -90°C and manganese halides (MnX_2, X= I, Br, Cl), even as their ate complexes $MnX_2 \bullet 2LiX$ (X= Br, Cl)[2a], are insoluble in the reaction mixture at this temperature. Therefore, the lithium-manganese exchange reaction only occurs at a higher temperature (-50 to -40°C with MnI_2) and, under these conditions, it is not possible to avoid the attack of the nitrile or the ester group by the aryllithium. To circumvent this limitation we have searched for a more convenient solvent and we have finally found that by working with the Trapp mixture (THF:ether:pentane 4:4:1)[8] the lithium-manganese transmetallation can be carried out at a lower temperature since between -90°C to -60°C the complexes $MnX_2 \bullet 2LiX$ (X= Br, Cl) are much more soluble in such a mixture than in ether or THF alone. In addition, the halogen-lithium exchange is also easier to carry out since the freezing point of the reaction mixture is lower. As an exemple, *p*-cyanobromobenzene **6** has been treated with BuLi at -100°C then the resulting organolithium was converted to *p*-cyanophenylmanganese chloride or bromide **7** by addition of $MnCl_2 \bullet 2LiCl$ or $MnBr_2 \bullet 2LiBr$ (1 equiv.) as a THF solution at -90°C. It is important to note that the best result was obtained with $MnBr_2 \bullet 2LiBr$ which is the most soluble under these conditions (Scheme 4).

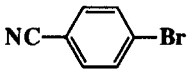
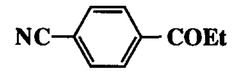
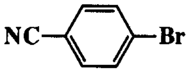
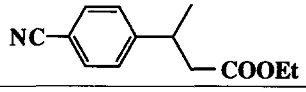
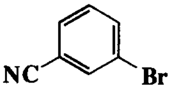
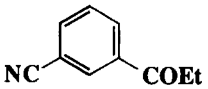
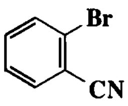
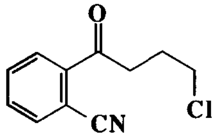
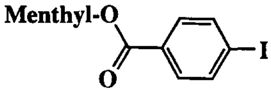
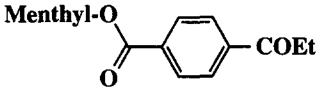
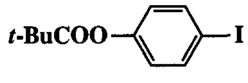
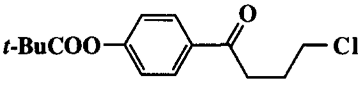
Scheme 4.



According to the same procedure, we have prepared various functionalized arylmanganese compounds from *p*, *m*, and *o*-bromobenzonitrile (Table 2, entries 1 to 4), menthyl *p*-iodobenzoate (entry 5) and *p*-iodophenyl pivalate (entry 6). It should be noted that only hindered ester groups such as menthyl ester or pivalate are tolerated. With the less hindered esters such as ethyl *p*-iodobenzoate, the lithium-halogen exchange and the 1,2-addition compete (about 20% of alcohol) moreover, after addition of $MnBr_2 \bullet 2LiBr$ the reaction mixture turns dark and the reaction with various electrophiles (I_2, RCOCl, ...) was unsuccessful. In all cases, ethylbenzoate was isolated as the main product.

In conclusion, we report above the first preparation of functionalized aryl and alkenylmanganese halides, a new class of organometallic reagents for the elaboration of polyfunctionalized molecules. They are obtained from the corresponding functionalized aryl and alkenylhalides according to a one-pot two step procedure: halogen-lithium exchange at low temperature then lithium-manganese transmetallation.

Table 2. Preparation of Arylmanganese Compounds Bearing a Cyano or an Ester Function.[a]

Entry	Aryl Halide	Electrophile[b]	Product	Yield (%)[c]
1		EtCOCl		80
2		MeCH=CHCOOEt		61
3		EtCOCl		78
4		$Cl(CH_2)_3COCl$		76
5		EtCOCl		62
6		$Cl(CH_2)_3COCl$		60

a/ General Procedure: A solution of BuLi in hexane or EtLi in ether (7.5 mmoles) is added dropwise to a solution of functionalized aryl halide (7.5 mmoles) in 25 ml of Trapp mixture at -100°C. After 5 min., a solution of $MnBr_2 \cdot 2LiBr$ in 10 ml of THF is introduced then the reaction mixture is allowed to warm to -60°C and is stirred for 5 min. b/ 0.85 equiv. of electrophile was used. The acylation reactions[9] were performed in the presence of 3% CuCl (-60°C to -10°C). The 1,4 addition to ethyl crotonate[10] was achieved in the presence of 3% CuCl and 1 equiv. of Me_3SiCl (-60°C to -10°C). c/ Yield of isolated product.

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5. a/ Parham, W. E.; Bradsher, C. K. *Acc. Chem. Res.* **1982**, *15*, 300-305. b/ Cahiez, G.; Bernard, D. and Normant, J. *Synthesis* **1976**, 245-248. c/ Tuker, C.E.; Majid, T.N.; Knochel, P. *J. Am. Chem. Soc.* **1992**, *114*, 3983-3985.
6. MnI_2 is slighly soluble in ether at 20°C. When the Li-Mn transmetallation reaction is performed under classical conditions (-10°C to 0°C) the presence of LiX facilitates the solubilisation of MnI_2 in the reaction mixture.
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