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ORGANOMANGANESE (II) REAGENTS XIII[1] : HIGHLY SELECTIVE ADDITION OF ORGANOMANGANESE HALIDES TO ALDEHYDES IN THE PRESENCE OF KETONES

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Summary *: Organomanganese halides add quite selectively to aldehydes in the presence of ketones to give the corresponding secondary alcohols in excellent yields.*

Organolithium or organomagnesium reagents generally do not discriminate between two carbonyl groups (i.e. keto-aldehydes) or between a carbonyl group and other functionalities.

For this purpose, various organotransition metal compounds have been studied (B, Sn, Cu, Cr, Mo, Ta, Nb, Hf, Ce, Pr, Nd, Sm, Gd, Sc, Y, La, Zr and Ti)[2,3] but until now, the best results have been indeniably obtained by means of organotitanium reagents[3].

For our part, we have previously shown that organomanganese compounds react very chemoselectively on a vast array of functional carboxylic acid chlorides or anhydrides (RCOOCOR, RCOOCOOEt ...) to give the corresponding functional ketones in high yields, under very mild conditions (usually -10°C to 20°C)[4]. On the other hand, we have also shown that organomanganese iodides, which easily add to aldehydes as well as ketones at 20°C, are able to react selectively with an aldehyde in the presence of a ketone at -50°C[5].

$$\mathrm{BuMnI} + \mathrm{MeCO(CH_2)_3CHO} \xrightarrow{\text{Ether, } -50^\circ\mathrm{C}} \mathrm{MeCO(CH_2)_3CHOHBu} \qquad 78\%$$

In this Letter, we describe further chemoselective additions of organomanganese reagents to various carbonyl derivatives.

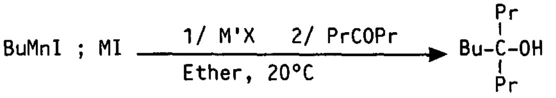
Organomanganese iodides 1 and 2 are prepared by transmetallation from organolithium or organomagnesium compounds[4b,c].

$$\mathrm{RLi} + \mathrm{MnI_2} \longrightarrow \mathrm{RMnI}\ ;\ \mathrm{LiI} \qquad \underline{1}$$

$$\mathrm{RMgX} + \mathrm{MnI_2} \longrightarrow \mathrm{RMnI}\ ;\ \mathrm{MgXI} \qquad \underline{2}$$

The nature of the salts generated during the preparation of the reagents 1 and 2 deeply influences their addition rates to a carbonyl group. Thus, the formation of the alcohol 3 from 4-heptanone is much more rapid in the presence of magnesium halides (Table I, entries 2 to 4) than in the presence of lithium halides (entry 1). This effect is probably due to an electrophilic activation of the carbonyl group by the magnesium salts.

Table I - Addition rate of butylmanganese iodide to 4-heptanone in ether ; influence of the magnesium and lithium salts



$$\mathrm{BuMnI\ ;\ MI} \xrightarrow[\text{Ether, 20°C}]{\text{1/ M'X} \quad \text{2/ PrCOPr}} \mathrm{Bu{-}\overset{\displaystyle Pr}{\underset{\displaystyle Pr}{C}}{-}OH}$$

3

			Yield (%) of ^{b}					
Entry	BuMnI ; MI	$M'X^{a}$	5 min	10 min	20 min	30 min	2.5 hrs	6 hrs
1	BuMnI ; LiI^{c}	none	-	34	48	53	63	80
2	BuMnI ; MgBrI^{d}	"	78	81	89	99		
3	BuMnI ; MgBrI	LiBr^{a}	-	80	-	-		
4	BuMnI ; LiI	$MgBr_2{}^{a}$	-	83	-	87		

a/ These salts have been added prior to the introduction of 4-heptanone as ethereal solutions. **b/** GLC yields. **c/** Prepared from BuLi. **d/** Prepared from BuMgBr.

Thus, the selective addition of organomanganese reagents to aldehydes in the presence of ketones has been reexamined. As expected, this addition, previously performed in ether at -60°C with organomanganese iodides prepared from organomagnesium compounds such as **4**[5], is now easily achieved at room temperature with an excellent selectivity by means of organomanganese iodides issued from organolithium compounds such as **5**[6].

$$\mathrm{BuMgBr} \xrightarrow{\mathrm{MnI_2}} \underset{\textbf{4}}{\mathrm{BuMnI\ ;\ MgBrI}} \xrightarrow[\text{Ether, -60°C}]{\mathrm{HexCHO + PrCOPr}} \underset{93\%\ ^{a,b}}{\mathrm{HexCHOHBu}} + \mathrm{PrCOPr}$$

$$\mathrm{BuLi} \xrightarrow{\mathrm{MnI_2}} \underset{\textbf{5}}{\mathrm{BuMnI\ ;\ LiI}} \xrightarrow[\text{Ether, 20°C}]{\mathrm{HexCHO + PrCOPr}} \underset{86\%\ ^{a,c}}{\mathrm{HexCHOHBu}} + \mathrm{PrCOPr}$$

a/ Isolated yields. **b/** Selectivity : 96%. **c/** Selectivity >99%, $Bu(Pr)_2COH$ was not detected by GLC.

In ether, organomanganese bromides e.g. **6** can be employed in place of their iodide analogous since they behave quite similarly toward carbonyl derivatives.

$$\mathrm{BuLi} \xrightarrow[\text{Ether, 0°C}]{\mathrm{MnBr_2}} \underset{\textbf{6}}{\mathrm{BuMnBr\ ;\ LiBr}} \xrightarrow[\text{20°C}]{\mathrm{HexCHO + PrCOPr}} \mathrm{HexCHOHBu} + \mathrm{PrCOPr}$$

93% (selectivity >99%)

These reagents (RMnBr) present the advantage of being prepared from organolithium compounds and manganese bromide. Indeed, from a practical point of view, anhydrous manganese bromide is commercially available and cheaper than manganese iodide.

The selective attack of an aldehyde in the presence of a ketone can also be performed in THF, at room temperature, with organomanganese chlorides[7] e.g. 7.

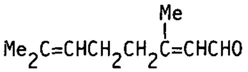
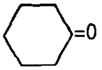
$$\mathrm{BuLi\ \ or\ \ BuMgX} \xrightarrow[0\ \mathrm{to}\ 20°\mathrm{C}]{\mathrm{MnCl_2}^{a}\ ;\ \mathrm{THF}} \underset{\mathbf{7}}{\mathrm{BuMnCl\ ;\ MCl}^{b}} \xrightarrow{\mathrm{HexCHO\ +\ PrCOPr}} \underset{90\%\ ^{c}}{\mathrm{HexCHOHBu}} \mathrm{\ +\ PrCOPr}$$

a/ $MnCl_2$ or $MnCl_4Li_2$[8]. **b/** MCl = LiCl or MgXCl. **c/** Selectivity >99%.

Further examples of aldehyde-ketone competitions are presented in the following table.

Table II - Selective addition of organomanganese halides RMnX to aldehydes in the presence of ketones

$$R_1CHO + R_2COR_3 \xrightarrow{RMnX^{a,b}} RR_1CHOH + R_2COR_3$$
$$(\text{aldehyde selectivity} > 99\%)^{c}$$

Entry	R_1CHO	R_2COR_3	R(of RMnX)	RR_1CHOH^{d} Isolated yield (%) from	
				RMnBr	RMnCl
1	 $Me_2C{=}CHCH_2CH_2C(Me){=}CHCHO$	PrCOPr	Me	90	91
2	PhCHO	"	Me	90	93
3	t-BuCHO	"	Hept	87	86
4	HexCHO	"	Bu	93	90
5	"	"	Me	95	88
6	"	"	Ph	94	88
7	"	"	$Me_2C{=}CH$	98	88
8	"	"	BuC≡C	80(99)[e]	72(85)[e]
9	"	"	i-Pr	-	71[f]
10	"	PentCOMe	Bu	96	95
11	"	PhCOPr	Bu	95	90
12	"	$Me_2C{=}CHCOHept$	Bu	90	95
13	"		Bu	88[c]	81[c]

a/ RMnBr/ether was prepared from RLi and RMnCl/THF from RLi or RMgX. **b/** Ratio aldehyde/ketone/RMnX : 1/1/1.05. Reaction time : 20 min. to 2 hrs. **c/** The formation of the tertiary alcohol derived from ketone has never been detected by GLC or NMR analysis, excepted in the case of the heptanal-cyclohexanone competition (entry 13 ; aldehyde-selectivity : 97% (ether) and 92% (THF). **d/** All secondary alcohols have been isolated by distillation. Yields are not optimized. **e/** This secondary propargylic alcohol partially decomposes during the distillation. GLC yields are given in brackets. **f/** In this case the side formation of HexCHOHCHOHHex is observed.

The competition experiments listed in Table II show that n or s-alkyl, alkenyl, aryl and alkynyl manganese halides are always completely aldehyde-selective at room temperature, in ether (RMnBr, entries 4 to 9) as in THF (RMnCl, entries 4 to 9). Thus, aliphatic (n or t-alkyl), ethylenic and aromatic aldehydes have been selectively converted, in high yields, into the corresponding secondary alcohols (entries 1 to 4) in the presence of aliphatic, ethylenic or aromatic ketones (entries 4 and 10 to 13).

These results can be advantageously compared to those which have been obtained with organotitanium compounds[3]. Indeed, the chemoselectivities are comparable ($>$99%) but the scope of the reaction is wider with organomanganese reagents since, for instance, alcenyl and s-alkyl manganese halides are used without drawback, contrary to their titanium counterparts. Moreover, the isolated yields indicated in Table II are often higher to those reported with organotitanium compounds (generally 5 to 10% or more).

Finally, it should be noted that the same selectivity is observed for intermolecular and intramolecular competition experiments.

$$\mathrm{EtCO(CH_2)_9CHO} \;+\; \mathrm{BuMnX} \xrightarrow{20^\circ\mathrm{C}} \mathrm{EtCO(CH_2)_9CHOHBu}$$

BuMnBr, ether : 90%

BuMnCl, THF : 89%

In conclusion, organomanganese derivatives are excellent reagents for the chemoselective addition to keto-aldehydes.

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6. Concerning the experimental procedure, it is noteworthy that the aldehyde-ketone mixture, which must be added at once between -60 and -80°C in the case of RMnI;MgBrI, can be introduced dropwise at 0°C when RMnI;LiI or RMnBr;LiBr are used. This considerable improvement, due to a clear enhancement of the selectivity, allows to carry out very easily the reaction on a large scale.
7. In THF, organomanganese reagents do not add 1-2 to ketones but only to aldehydes. Accordingly, the chemoselective addition to aldehyde-ketone mixtures can be indifferently performed with RMnCl issued from RLi or RMgX.
8. This complex is easily prepared, as a solution, by mixing $MnCl_2$ + 2LiCl in THF at 20°C.

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