Tetrahedron Letters,Vol.27,No.37,pp 4441-4444,1986   0040-4039/86 $3.00 + .00
Printed in Great Britain   Pergamon Journals Ltd.

ORGANOMANGANESE (II) REAGENTS XII[1] :
AN EFFICIENT ONE-POT PREPARATION OF UNSYMMETRICAL SECONDARY OR TERTIARY ALCOHOLS

G. CAHIEZ*, J. RIVAS-ENTERRIOS, H. GRANGER-VEYRON

Laboratoire de Chimie des Organoéléments, U.A. 473, tour 44-45
Université P. & M. Curie, 4 place Jussieu F-75252 PARIS Cédex 05

Summary *: Various unsymmetrical secondary or tertiary alcohols have been prepared in high yields by an efficient one-pot procedure involving the acylation of an organomanganese reagent by an acyl chloride and the addition to the ketone formed of various organometallic compounds (RLi, RMgX, $LiAlH_4$, $NaBH_4$). The complexation of the intermediate ketone by the metallic salts present in the reaction mixture allows to perform the 1-2 addition step under exceptionally mild conditions (0 to 20°C).*

In the field of organometallic chemistry, acylation of organomanganese reagents is one of the most suitable methods to prepare, under mild conditions, a large variety of ketones in high yields. Thus we have recently reported that saturated, ethylenic, acetylenic and aromatic ketones, bearing or not various functional groups (e.g. Cl, OR, SR, COOR, CN, COR), are easily obtained in this way.[2]

$$RLi \quad or \quad RMgX \xrightarrow[0°C\ to\ RT,30min]{MnX_2} RMnX \xrightarrow[-10°C\ to\ RT,30min\ to\ 4hrs]{R'COZ} RCOR'$$

X = I,Br(Ether) or Br,Cl(THF)   RCOZ = RCOCl ; RCOOCOOEt ; $(RCO)_2O$

The ketones prepared according to these reactions are never accompanied by the corresponding tertiary alcohols.[3]

$$RCOZ \xrightarrow{RMnX} RCOR \cancel{\xrightarrow{RMnX}} R_3COH \quad \underline{1}$$

Concerning the acylation of organomanganese iodides by carboxylic acid chlorides, we have shown that ketones are likely formed in situ before hydrolysis as a complex with the metallic salts present in the reaction mixture (MnX_2 ; LiX or MnX_2 ; MgX_2)[4]. At first sight, this was very surprising since the reaction rates of organomanganese iodides with acyl chlorides and ketones respectively did not seem different enough to prevent the formation of the carbinol 1 as a side product (Table I).

Table 1 - Reaction of butyl manganese iodide with 4-heptanone and pentanoyl chloride

$$\underline{3} \quad BuCOBu \xleftarrow{BuCOCl\ ;\ Ether,RT} BuMnI^{a} \xrightarrow{Pr_2C=0} Bu(Pr)_2COH \quad \underline{2}$$

Time (min) :	5	10	30
Yield(%) of alcohol 2	78[b]	81[b]	90[c]
Yield(%) of ketone 3	80[b]	92[c]	

a/ BuMnI was prepared from BuMgBr and MnI_2 ; **b/** GLC yields ; **c/** isolated yields.

Unexpectedly, the absence of alcohol 1 is due to the complexation of the ketone. Indeed, organomanganese iodides add much more slowly on the complexed ketones e.g. 4 than on the uncomplexed ones (Table II).[6]

Table II - Reaction rates of butyl manganese iodide with complexed and uncomplexed 5-nonanones 4 and 5 in ether.

$$\mathrm{BuMnI(MgBrI)}^{a} + \mathrm{BuCOCl} \longrightarrow \underset{\mathbf{4}}{\mathrm{BuCOBu(MnICl\ ;\ MgBrI)}} \xrightarrow[\text{Ether, RT}]{\text{BuMnI}} \mathrm{Bu_3COH}$$

$$\underset{\mathbf{5}}{\mathrm{BuCOBu}} \xrightarrow[\text{Ether, RT}]{\text{BuMnI}^{a}} \mathrm{Bu_3COH}$$

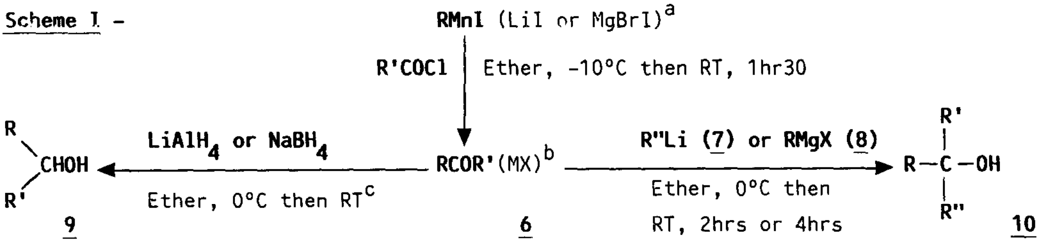
Time (hr)	Yield(%)^{b} of $\mathrm{Bu_3COH}$ from : complexed BuCOBu (4)	BuCOBu (5)
0.2	0^{c}	81
0.5	0	99
36	63^{d}	-

a/ BuMnI was prepared from BuMgBr and $\mathrm{MnI_2}$; b/ GLC yields ;
c/ GLC yield of 5-nonanone : 92% ; d/ 22% of 5-nonanone are recovered after 36hrs.

Interestingly, this complexation also influences the addition rate of organolithium and organomagnesium reagents[7]. Thus, ketones react with organolithium compounds in about 30min at -78°C[8] whereas complexed ketones such as 4 react in 30min to 1hr30 at 20°C.

This feature led us to develop an efficient and convenient method for the one-pot preparation of unsymmetrical secondary or tertiary alcohols.

Scheme I -



a/ prepared from RLi or RMgBr (0°C then 10°C to 20°C, 30min) ;
b/ MX = MnClI ; LiI or MnClI ; MgBrI ; c/ for $\mathrm{NaBH_4}$: 12hrs, for $\mathrm{LiAlH_4}$: 2hrs.

Our results listed in Table III show that high yields of isolated alcohols 9 and 10 were generally obtained according to the above methodology (scheme I). The wide synthetic scope of the first stage of this reaction has already been described in details[2]. In the second stage, various organometallic reagents can add 1,2 to the complexed ketone 6. Thus, organolithium reagents 7 as well as organomagnesium compounds 8 (prepared in ether or in THF) led to the tertiary alcohols 10 (entries 1 to 17) whereas lithium aluminium hydride or sodium borohydride gave the secondary alcohols 9 (entries 18 and 19).

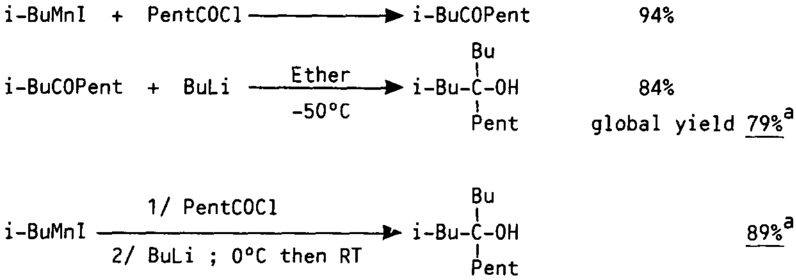
The yield of carbinol 10 was lowered in two cases :

- with conjugated ethylenic and acetylenic ketones (entries 9 and 10) due to a competition between 1,2-addition and manganese-catalyzed polyaddition processes.[1]
- with hindered ketones and with bulky organometallic compounds (entries 7 and 8) owing to

side reactions such as enolization and reduction (these also occur in the absence of manganous salts).[10]

In conclusion, this new synthetic method allows to prepare numerous unsymmetrical secondary or tertiary alcohols in high yields under very mild conditions since all steps are carried out between -10°C and 20°C. This is especially noteworthy for the last step which involved the addition of organomagnesium as well as organolithium reagents at 0°C.

Finally, by comparison with the classical procedure in which the intermediate ketone is isolated, the one-pot preparation described above requires less time and gives better yields.



$$\text{i-BuMnI} + \text{PentCOCl} \longrightarrow \text{i-BuCOPent} \qquad 94\%$$

$$\text{i-BuCOPent} + \text{BuLi} \xrightarrow[\text{-50°C}]{\text{Ether}} \text{i-Bu-}\overset{\text{Bu}}{\underset{\text{Pent}}{\text{C}}}\text{-OH} \qquad 84\% \quad \text{global yield } \underline{79\%}^{a}$$

$$\text{i-BuMnI} \xrightarrow[\text{2/ BuLi ; 0°C then RT}]{\text{1/ PentCOCl}} \text{i-Bu-}\overset{\text{Bu}}{\underset{\text{Pent}}{\text{C}}}\text{-OH} \qquad \underline{89\%}^{a}$$

a/ All reactions were performed on a 50 mmoles scale.

Further applications to the synthesis of natural or pharmaceutical products will be reported elsewhere.

Table III - One-pot preparation of unsymmetrical tertiary or secondary alcohols **10** and **9**

Entry	R	R'	R"Li or R"MgX[a]	Isolated yield (%) of **10** or **9**
1	Hept[c]	Et	BuLi	83
2	Hept[c]	Et	BuMgBr	85
3	Hept[c]	Et	BuMgCl	81
6	Bu[d]	i-Bu	MeLi	80
4	i-Bu[c]	Pent	BuLi	89
5	i-Bu[c]	Pent	BuMgBr	83
7	Et[d]	t-Bu	BuLi	53-72[e]
8	Et[d]	t-Bu	s-BuLi	35
9	Bu[d]	$Me_2C=CH$	EtLi	61
10	BuC≡C[d]	i-Pr	EtLi	40
11	Hept[c]	Ph	MeLi	89
12	Bu[c]	Pent	$Me_2C=CHMgBr$	79
13	Bu[c]	Hex	MeCH=CHMgBr	72.5
14	Bu[d]	Pent	MeCH=CHMgBr	70
15	Bu[d]	i-Bu	PhLi	73
16	Bu[c]	i-Bu	PhMgCl	68
17	Bu[d]	i-Bu	$CH_2=CHCH_2MgBr$	80
18	i-Bu[c]	Pent	$LiAlH_4$	84.5[f]
19	Hept[c]	i-Bu	$NaBH_4$	91[f,g]

a/ R"Li were used as solution in ether or hydrocarbons, R"MgBr in ether, R"MgCl, MeCH=CHMgBr and Me_2C=CHMgBr in THF. For experimental conditions see Scheme 1 ; **b/** ratio RMnI/R'COCl/R"Li or R"MgX : 1/1/1.25. The yields are based on the starting products : RMnI and R'COCl. All products were isolated by distillation ; **c/** RMnI prepared from RMgBr ; **d/** RMnI prepared from RLi ; **e/** A second addition of BuLi, after methanolysis of the reaction mixture, allowed to improve the yield of tertiary alcohol (53 to 72%). This result shows that enolization occurs in a large extent with hindered ketones ; **f/** Molar ratio RMnI/R'COCl/$LiAlH_4$ or $NaBH_4$: 1/1/0.31. ; **g/** $NaBH_4$ was used as a solution in ethanol (0.25 mole/l).

References and Notes

1. Part XI : G. Cahiez, M. Alami, Tetrahedron Letters, 1986, 569.
2. G. Friour, G. Cahiez, J. Normant, Synthesis, 1984, 37 and 1985, 50.
   For a general survey : G. Cahiez, l'Actualité Chimique, 1984, 9, 24 and G. Cahiez, J.F. Normant, Modern Synthetic Methods 1983, R. Scheffold, Ed., J. Wiley and Sons, Inc., Chichester, 1983, 3, 173.
3. The side formation of carbinol was only observed in some cases when methyl manganese iodide was used.
4. G. Cahiez, unpublished results.
   The in situ formation of a ketone-metallic salts complex is supported by the investigations summarized below. During the acylation of organomanganese reagents (RMnX) by acyl chlorides (R'COCl) in ether, a pasty precipitate (or less frequently a heavy oil) is always formed. In the case of R=R'=Bu, the precipitate which has been separated by decantation presents the following features :
   - it gave, after hydrolysis, 92 to 100% of the total amount of 5-nonanone resulting from the reaction (on several runs, 0 to 8% of BuCOBu are recovered in the supernatant) ;
   - its IR spectrum exhibits a strong band to 1695cm^{-1}. Such a lowering of the C=O stretching frequency is certainly due to the complexation of the 5-nonanone with the metallic salts present in the reaction mixture. It should be noted that a similar effect is well known for various ketones-Lewis acid complexes (e.g. ketone-HgX_2, ZnX_2; see note 5)
   - lastly we have shown that 5-nonanone is progressively released from the precipitate when this latter is suspended in pentane, then treated with increasing amounts of various ligands, under anhydrous conditions, at 20°C :

Ligand (number of equivalents) :	Et_3N (5)	Et_3N (10)	Et_3N (15)	MeCOMe (10)
5-nonanone % in the supernatant	40.5	76.5	97	100

5. For the IR study of ketone-metallic salt complexes see :
   a/ B.P. Susz, P. Chalendon, Helv. Chim. Acta, 1958, 41, 1332 and references quoted in this communication.
   b/ C. Georgoulis, B. Gross, J.C. Ziegler, C. Prévost, C.R.Acad.Sci. C, 1968,266,1465
   Such complexes have also been isolated, for instance : B.N. Menshutkin, J. Russ. Phys. Chem. Soc., 1906, 38, 1317 and 1335 (ketone-MgX_2) ; see also reference 5a (ketone-$ZnCl_2$).
6. This decrease of the reaction rate may be due to the heterogeneity of the reaction mixture which results from the precipitation of the complexed ketone. However it should be noted that the presence of manganous salts may also decrease the addition rate of organomanganese reagents on ketones by altering the nature of the organomanganese reagents or of intermediates involved in the addition process. This assumption is proposed by analogy with the results of several investigations devoted to a very similar case : the rate depressing effect of magnesium bromide on the reaction of organomagnesium reagents with ketones. Indeed, although the interpretation of this effect has given rise to much controversy, all these studies have shown that the addition of magnesium bromide affects the course and the kinetics of the addition. See inter alia : M. Anteunis, J. Org. Chem., 1961, 26, 4214 and 1962, 27, 596 ; H.O. House, D.D. Traficante, J. Org. Chem., 1963, 28, 355 ; N.M. Bikales, E.I. Becker, Can. J. Chem., 1963, 41, 1329 ; R. D'Hollander, M. Anteunis, Bull. Soc. Chim. Belges, 1965, 74, 71 ; S.G. Smith, G. Su, Tetrahedron Letters, 1966, 4417 ; M. Chastrette, R. Amouroux, Bull. Soc. Chim. Fr., 1970, 4342 ; E.C. Ashby, Pure and Appl; Chem. 1980, 545.
7. Organomanganese reagents are very likely partially formed as intermediates during these reactions.
8. E.C. Ashby, S. Anoding, J. Org. Chem., 1979, 44, 4371.
9. For organomagnesium reagents see : F.C. Whitmore, R.S. George, J. Am. Chem. Soc., 1942, 64, 1239. For organolithium reagents see : J.D. Buhler, J. Org. Chem., 1973, 38, 904.

(Received in France 30 June 1986)