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ORGANOMANGANOUS REAGENTS VII[1] :

Organomanganous iodides as selective reagents for synthesis of multifunctional ketones. Application to steroid chemistry

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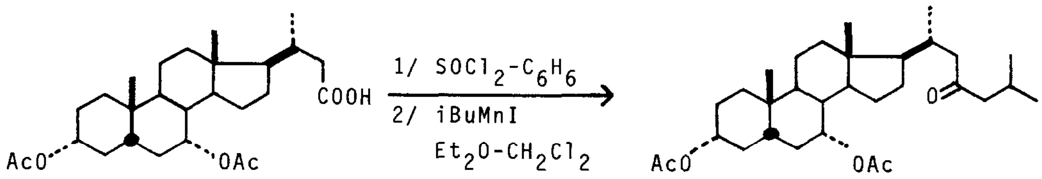
Summary :
Ketosteroids substituted by formyloxy, acetoxy or carbonyl groups are obtained in high yields by chemoselective reaction of organomanganous iodide reagents on the corresponding carboxylic acid chlorides.

Preparation of polyfunctional ketones from polyfunctional carboxylic acids by the organometallic way is often difficult, especially when other carbonyl functions such as esters or ketones are present.

These last years, organocuprates (or copper) derivatives have been the most common reagents for this purpose but they are expensive (4 to 6 equivalents of starting RLi are needed in order to prepare 2 or 3 equivalents of cuprate reagent per acid chloride)[2] and their chemoselectivity is very dependent on the reaction time and requires the use of a low temperature (-78°C).

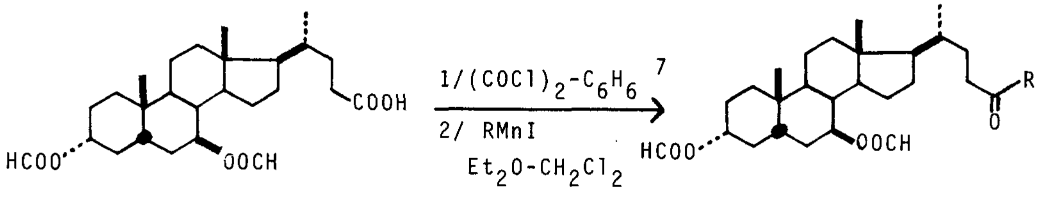
Recently organomanganous iodides have been reported as very selective and cheap[3] reagents (stoechiometric amounts of RMnI are used) for the preparation under mild conditions (-10°C to RT) of various functional ketones in high yields via carboxylic acid chlorides[4] ; however this method has not been used for the elaboration of complex products.

The synthesis of keto-steroids (2,4,6,8) from the corresponding carboxylic acids (1,3,5,7) is now reported with the use of organomanganous iodides reagents for key steps :



1[5]

2 93%



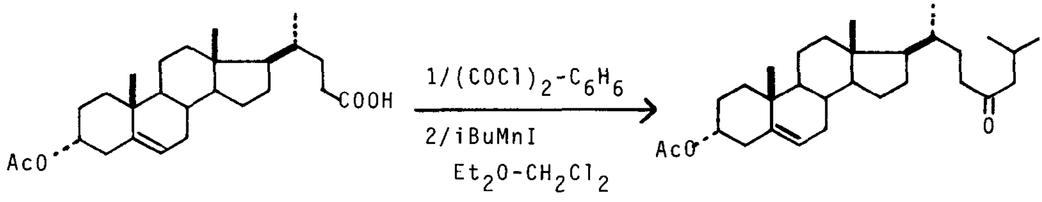
3[6]

4

a/ R= iBu- 89%

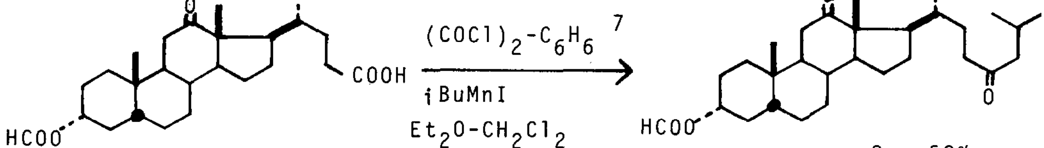
b/ R= $Me_2C=CH-$ 78,5%

c/ R= Pr–C≡C- 73,5%



5

6 87%



7

8 52%

General procedure :

A solution of crude acid chloride in CH_2Cl_2 (for the use of thionyl or oxalyl chlorides see footnote 7) is added at -30°C to the suspension of 1.1. equivalent of RMnI in ether ($\simeq$1 M/1 ; for the preparation of RMnI see reference 4). After 15min, the mixture is allowed to warm to room temperature ; it is stirred for 3h then quenched with HCl 1 N solution, decanted, extracted with CH_2Cl_2(or Et_2O), dried ($MgSO_4$) and the solvents are removed in vacuo. The product is chromatographically isolated, then recristallized.

All products give satisfactory microanalyses and spectral data (IR, UV, RMN) are in good accordance with the assigned structures .

2	93%	(13g)	; M.P=124°C(hexane) ; $(\alpha)_D=+13,5°$ -1% $CHCl_3$
4a	89%	(8,7g)	; M.P=116°C (hexane); $(\alpha)_D=+47,5°$ -1% $CHCl_3$
4b	78,5%	(7,65g)	; M.P=120°C(hexane) ; $(\alpha)_D=+41,5°$ -1% $CHCl_3$
4c	73,5%	(22,9g)	; viscous oil
6	87%	(5,95g)	; M.P=111°C(cyclohexane) $(\alpha)_D=-41,5°$ -1% $CHCl_3$
8	52%	(5,1g)	; M.P=156°C(hexane) ; $(\alpha)_D=+106°$ -0,6% $CHCl_3$

The preparation of ketones 2, 4a, 4b, 4c, 6 which are obtained in excellent yields of isolated products (73-93%) shows the very good selectivity of attack of the organomanganous reagents on acid chlorides and acetoxy or formyloxy groups in spite of the reactivity of formic esters with organomanganous iodides[1]. A more drastic competition occurs with keto acid derivative 7 which gives nevertheless the corresponding keto compound 8 with 52% yield in spite of the very high reactivity of the carbonyl group. (In fact, ketones which are reported to react with RMnI very quickly at -60° in ether seem more reactive than acid chlorides)[4,8]. Addition of organomanganous iodide to the acid chloride solution (inverse addition) or use of the acid bromide instead of the chloride did not improve the yield of ketone 8.

These last results show that the selectivity observed between the carbonyl and the acid chloride (or bromide) during the attack of the keto acid chloride 7 is independent of the difference of the reactivity between these two independent functional groups. This point is presently studied.

Another illustration of the chemoselectivity of organomanganous iodides is the use of methylene chloride as co-solvent for all the reactions reported above (acid chlorides of 1, 3, 5, 7 are very little soluble in ether).

It is very important to remark that this solvent which reacts with most organometallic derivatives is inert toward organomanganous iodides and can be used without problem.

These syntheses, which are performed on a large scale (5 to 23g) show that organomanganous derivatives are very convenient and efficient reagents for the elaboration of complex ketones in high yields.

Aknowledgments :

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Notes and References :

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3/ Manganese is one of the less expensive metals

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5/ This compound is obtained from chenodesoxycholic acid by Barbier-Wieland degradation

6/ Treatment of ursodesoxycholic acid by formic acid for 4h at 60°C gives the formylated acid 3 in 90% isolated yield. Perchloric acid is not necessary to perform this reaction as is reported by :

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7/ Treatment of carboxylic acids 3 and 7 by thionyl chlorides gives poor yields of acid chloride derivatives ($<$50%) but oxalyl chloride performs quantitatively this transformation

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