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Cp_2TiCl_2-CATALYZED GRIGNARD REACTIONS. 3. REACTIONS WITH ESTERS: EFFICIENT METHODOLOGY FOR THE SYNTHESIS OF SECONDARY ALCOHOLS AND FOR THE REDUCTION OF ESTERS TO PRIMARY ALCOHOLS[1]

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Summary: Cp_2TiCl_2-catalyzed Grignard reactions with esters provide general methodology for preparation of secondary alcohols or for reduction of esters to the corresponding primary alcohols.

In the preceeding paper we revealed that the path of Grignard reactions with ketones or aldehydes was changed greatly by catalysis of Cp_2TiCl_2, proceeding to reduction of ketones or aldehydes to the corresponding alcohols[1]. This led us to assume that other Grignard reactions which proceed readily under mild conditions would similarly be influenced.

Here reported are some unexpected and synthetically useful results from the investigation of Cp_2TiCl_2-catalyzed Grignard reactions with esters.

The normal reactions of Grignard reagents with esters give tertiary alcohols (eq. 1)[2]. When this reaction was carried out in the presence of a catalytic amount of Cp_2TiCl_2, it was found that the reaction proceeded according to eqs. 2 or 3 depending on the amount of the catalyst.[3]

$$R^1COOR' + 2\ R^2MgX \longrightarrow R^1R^2_2COMgX \qquad (1)$$

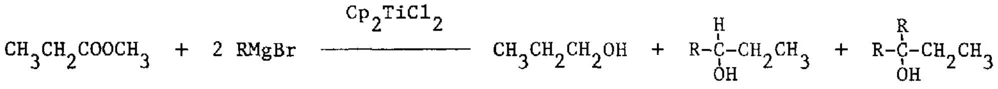
$$R^1COOR' + 2\ R^2MgX \longrightarrow R^1R^2HCOMgX \qquad (2)$$

$$R^1COOR' + 2\ R^2MgX \longrightarrow R^1CH_2OMgX \qquad (3)$$

The reaction proceeded according to eq. 2 at low content of Cp_2TiCl_2, but according to eq. 3 at higher catalyst contents.
It is, therefore, possible to choose either reaction paths 2 or 3 by changing the catalyst content. However, the optimum quantity of Cp_2TiCl_2 appears to depend on the reagents. As shown in Table 1, $CH_3CH_2COOCH_3$ reacted with C_3H_7MgBr in the presence of 1 mol% of Cp_2TiCl_2 to afford 3-hexanol (90%) and propanol (9%) in 97% total yield. When the same reaction was carried out with higher catalyst content, the yield of propanol was increased and reached 78% at 8 mol% of

Cp_2TiCl_2. On the other hand, $(CH_3)_2CHCH_2MgBr$, which has more reducing power than C_3H_7MgBr, reacted with $CH_3CH_2COOCH_3$ in the presence of 2 mol% of Cp_2TiCl_2 to give propanol in 90% yield, and it is necessary to use as little as 0.1% of Cp_2TiCl_2 to increase the yield of the coupled alcohol, 5-methyl-3-hexanol.

TABLE 1. DISTRIBUTION OF THE REACTION PRODUCTS OF GRIGNARD REAGENT WITH $CH_3CH_2COOCH_3$ IN THE PRESENCE OF VARIOUS AMOUNTS OF Cp_2TiCl_2



$$CH_3CH_2COOCH_3 + 2\ RMgBr \xrightarrow{Cp_2TiCl_2} CH_3CH_2CH_2OH + R-\underset{OH}{\overset{H}{C}}-CH_2CH_3 + R-\underset{OH}{\overset{R}{C}}-CH_2CH_3$$

1 2 3

R in RMgBr	mol% of Cp_2TiCl_2 [a]	Product distribution[b] 1	2	3		Total yield[b] %
$CH_3CH_2CH_2$	0	4	0	96		99
	1	9	90	1		97
	4	50	50	0		96
	8	78	22	0		98
$(CH_3)_2CHCH_2$	0	0	60	36	c	86
	0.13	4	96	0		92
	1	73	27	0		99
	2	96	4	0		94

[a] Based on ester. [b] Determined by GLC. [c] 4% of $(CH_3)_2CHCH_2\underset{O}{\underset{\|}{C}}CH_2CH_3$ was coproduced.

Therefore it is desirable to use iso-butylmagnesium bromide in order to reduce esters to primary alcohols because small amounts of catalyst are sufficient.

The results of the reduction of esters to primary alcohols using iso-butylmagnesium bromide are summarized in Table 2, and Table 3 shows results of the preparation of secondary alcohols by coupling of various esters with Grignard reagents.

It can be seen from the observations that the reactions of various alkyl esters with Grignard reagents which have hydrogen atom on the β-carbon are greatly affected by the presence of Cp_2TiCl_2 and offer a convenient method for reducing esters to primary alcohols or to prepare the coupled secondary alcohols. However, as in the case of ketones and aldehydes[1], reactions with methyl or phenyl Grignard reagent, and ethyl Grignard reagent, despite having β-hydrogens, did not change their path by Cp_2TiCl_2. It is also known that in contrast to alkyl esters, reaction with aryl or α,β-unsaturated esters so far investigated, such as $C_6H_5COOCH_3$, $CH_2=CHCOOCH_3$ or $C_6H_5CH=CHCOOCH_3$, did not show different results from reaction in the absence of the catalyst.

TABLE 2. REACTIONS OF ESTERS WITH iso-BUTYLMAGNESIUM BROMIDE IN THE PRESENCE OF 2 mol% OF Cp_2TiCl_2[a]

Ester	Product	Yield (%)[b]
$CH_3CH_2COOCH_3$	$CH_3CH_2CH_2OH$	90[c]
$CH_3CH_2COOC_6H_5$	$CH_3CH_2CH_2OH$	94[c]
$CH_3(CH_2)_5COOCH_3$	$CH_3(CH_2)_5CH_2OH$	91
$CH_3(CH_2)_5COOC_2H_5$	$CH_3(CH_2)_5CH_2OH$	94
$(CH_3)_2CHCOOCH_3$	$(CH_3)_2CHCH_2OH$	84
$C_6H_5COOCH_3$	d	
$C_6H_5CH_2COOCH_3$	$C_6H_5CH_2CH_2OH$	92
$CH_2{=}CHCOOCH_3$	d	
$C_6H_5CH{=}CHCOOCH_3$	d	

[a] 30 mmol of ester, 63 mmol of the Grignard reagent and 0.6 mmol of Cp_2TiCl_2 in 65 ml of ether, for 1 h at room temperature. [b] Isolated yield by distillation. [c] GLC yield. [d] No primary alcohol was obtained; Reaction was not affected by Cp_2TiCl_2

TABLE 3. THE YIELDS OF SECONDARY ALCOHOLS FROM THE Cp_2TiCl_2-CATALYZED GRIGNARD REACTIONS WITH ESTERS[a]

Starting material		Catalyst content mol%[b]	Yield of R^1R^2CHOH[c] %
Ester R^1 in R^1COOCH_3	Grignard reagent R^2 in R^2MgBr		
C_6H_{13}	CH_3	1	d
C_6H_{13}	CH_3CH_2	1	d
C_2H_5	$CH_3CH_2CH_2$	1	83
C_6H_{13}		1	81
$(CH_3)_2CH$		1	75
$C_6H_5CH_2$		1	88
C_2H_5	$(CH_3)_2CH$	0.4	74[e]
C_2H_5	$(CH_3)_2CHCH_2$	0.13	85
CH_3[f]	C_6H_{13}	1	91
C_2H_5	C_6H_5	1	d

[a] 30 mmol of ester and 63 mmol of Grignard reagent in 50-70 ml of ether, for 1 h at room temperature. [b] Based on ester. [c] Isolated yield by distillation, and products were identified by NMR and GLC analysis by comparison with authentic samples. [d] No secondary alcohol was obtained, tertiary carbinol was usually obtained as in the case in the absence of catalyst. [e] Contained 4% of $CH_3CH_2CH_2CH(OH)CH_2CH_3$. [f] $CH_3COOC_2H_5$.

As we noted in the case of Cp_2TiCl_2-catalyzed Grignard reactions with ketones or aldehydes[1], the present reaction very likely involves the intermediacy of Cp_2TiH.

In conclusion, though there are some limitations on its applications to organic synthesis, the present reaction apparently offers a new valuable methodology for preparation of secondary alcohols[4] or for reduction of esters to primary alcohols.[5]

Further extension of Cp_2TiCl_2-catalyzed Grignard reactions to carboxylic acids, lactones and oxides is now undergoing and will be published before long.

References and Notes

1. Part 2: F. Sato, T. Jinbo, and M. Sato, Tetrahedron Lett., preceding article.
2. M.S. Kharasch and O. Reinmuth, "Grignard Reactions of Nonmetallic Substances," Prentice-Hall, New York, 1954, pp 549-708.
3. The reaction was carried out as follows; After 5 min stirring of an ether solution of Grignard reagent (2.1 equiv) and a catalytic amount of Cp_2TiCl_2 at 0°C, ester was added dropwise, and then the reaction mixture was stirred for 1 h at room temperature.
4. Though it is well known that Grignard reactions with aldehydes give secondary alcohols in excellent yields[6], the present method has the advantage that esters are more readily available than the corresponding aldehydes.
5. Because Grignard reagents are considerably less expensive than other metal hydride reagents which can be used for reduction of esters to primary alcohols, such as $LiAlH_4$[7], $LiBH_4$[8] and $LiEt_3BH$[8], the present method is economically attractive.
6. Ref. 2, pp 138-528.
7. J.S. Pizey, "Synthetic Reagents," vol. 1, John Wiley & Sons LTD., New York, N.Y., 1974, pp 127-141.
8. H.C. Brown and S. Krishnamurthy, Aldrichimica Acta, 12, 3 (1979).

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