

PREPARATION OF KETONES BY DIRECT REACTION OF GRIGNARD
REAGENTS WITH ACID CHLORIDES IN TETRAHYDROFURAN

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Summary: Grignard reagents react with acid chlorides in tetrahydrofuran at low temperature to produce ketones in excellent yields. The results reported here strongly indicate the importance of the solvent in Grignard reagent chemistry.

It has been generally accepted that the reaction of Grignard reagents with acid halides cannot be used for ketone synthesis because of the invariable accompaniment of the tertiary and/or secondary alcohols. It is therefore recommended to use in place of Grignard reagents the corresponding organo-zinc¹, cadmium², copper³, or rhodium⁴ compounds with acid chlorides for ketone synthesis. In another method, Mukaiyama, et. al. found that Grignard reagents react with S-(2-pyridyl)thiolates obtained by the reaction of acid halides with 2-pyridine-thiol to give the corresponding ketones in almost quantitative yields⁵. On the other hand, though not generally, addition of catalytic amounts of transition metal compounds, such as FeCl₃⁶, CuCl⁷, or excess hexamethylphosphorictriamide^{8,9} have been shown to improve the yields of ketones by direct reaction of Grignard reagents and acid halides.

Is it really impossible to prepare ketones by the standard method for Grignard

reagents with acid halides? Surprisingly, we have now found that Grignard reagents react with acid chlorides in tetrahydrofuran at low temperature to afford ketones in almost quantitative yields.

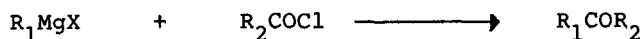
The reactions were carried out by standard methods, i.e., Grignard reagent in THF was added dropwise to a THF solution of excess acid chloride at low temperature. For example, to a solution of 29 mmol of butyryl chloride in 15 ml of THF was added dropwise over about 30 minutes a THF solution of hexylmagnesium bromide (20 ml of 0.72 M, 14.4 mmol) at -78°C . The reaction mixture was brought to room temperature over about one hour to give a clear solution. After addition of 30 ml of water the organic layer was extracted with ether. The extract was washed with 1N sodium hydroxide solution and brine and dried over MgSO_4 . GLC and ^1H NMR analysis of the residue after removal of the solvent showed almost pure 4-decanone. The residue was distilled to give 4-decanone in 95% yield.

In a similar manner, aromatic ketones and primary, secondary and tertiary aliphatic ketones were obtained in excellent yields as shown in Table 1. In all cases except a few (entries 4 and 12) the yields of tertiary and/or secondary alcohols were less than 1%. In contrast, when the same reactions were carried out in diethyl ether, secondary and/or tertiary alcohols were the main products, and the yields of ketones were low as shown in entries 2 and 8.

Though the reasons for the striking solvent effect in this reaction await further study, the difference in reactivity of Grignard reagents to acyl chlorides between THF and ether at low temperature is apparently significant. It was found that Grignard reagents react with acyl chlorides more rapidly in THF than in ether. The reaction of phenylmagnesium bromide with benzoyl chloride for 2h at -78°C followed by quenching of the reaction mixture with methanol at that temperature afforded benzophenone in 33% yield when the reaction was carried out in THF, whereas in ether solvent less than 5% of benzophenone with trace amounts of triphenylcarbinol was produced.

Several points relating to the application of the present reaction are worthy of comment. Results obtained so far demonstrate the sensitivity of the reaction to temperature variation. At room temperature, side reactions occurred and the

TABLE 1



Entry	R ₁ in R ₁ MgX	R ₂ in R ₂ COCl	Reaction conditions			Isolated yield ^b of R ₁ COR ₂ %
			Solvent	Molar ratio R ₂ COCl/R ₁ MgX	Temp ^a °C	
1	C ₆ H ₅ ^c	C ₆ H ₅	THF	1	-78	89
2		C ₆ H ₅	diethyl ether	1	-78	(39) ^{e,f}
3		p-ClC ₆ H ₄	THF	1	-78	71
4		CH ₃ CH ₂ CH ₂	THF	2	-78	71 ^g
5	p-CH ₃ C ₆ H ₄ ^c	C ₆ H ₅	THF	1	-78	84
6	CH ₃ CH ₂ CH ₂ ^d	C ₆ H ₅	THF	2	-78	86
7		CH ₃ CH ₂ CH ₂	THF	2	-78	80
8		CH ₃ CH ₂ CH ₂	diethyl ether	2	-78	(12) ^{e,h}
9		(CH ₃) ₂ CH	THF	2	-78	79
10		(CH ₃) ₃ C	THF	2	-78	88
11	(CH ₃) ₂ CH ^d	CH ₃ CH ₂ CH ₂	THF	2	-78	78
12	(CH ₃) ₃ C ^c	CH ₃ CH ₂ CH ₂	THF	2	-78	82 ⁱ
13	CH ₃ (CH ₂) ₄ CH ₂ ^c	CH ₃	THF	2	-78	95
14		CH ₃	THF	1.3	-78	93
15		CH ₃ CH ₂ CH ₂	THF	2	-78	95
16		CH ₃ CH ₂ CH ₂	THF	2	-50	93
17		CH ₃ CH ₂ CH ₂	THF	2	-30	92

^aTemperature for addition of Grignard reagent. ^bIsolated by column chromatography in the case of Entries 1, 3 and 5, and by distillation for other Entries.

^cGrignard reagent was prepared from bromide. ^dGrignard reagent was prepared from chloride. ^eGLC analysis. ^fOther product is triphenylcarbinol. ^gAround 10% of tertiary alcohol was co-produced. ^hOther products are secondary and tertiary alcohols. ⁱAround 5% of secondary and tertiary alcohols were produced.

yields of ketones decreased. However, in the case of the reaction of hexylmagnesium bromide with butyryl chloride (entries 15-17 in Table 1) there was no observable decrease in the yield when the addition temperature was changed from -78°C to -30°C . Though it is desirable in most cases to add the Grignard reagent dropwise to an excess of acyl chloride, for the reaction of phenylmagnesium bromide and benzoyl chloride (entry 1) there was no significant change in the yield of ketone when equimolar amounts of reagents were mixed at once at -78°C .

Thus although the optimum and economic conditions for this reaction appear to depend on the reagents, it is easy to obtain them experimentally for the required cases.

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