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INVESTIGATION OF OPTIMAL CONDITIONS FOR THE SYNTHESIS OF HINDERED ALIPHATIC KETONES. CATALYTIC ORIENTATION OF THE CONDENSATION OF RLi OR RMgX- R'COCl BY CUPROUS HALIDES .

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The synthesis of aliphatic ketones has given rise to a number of publications that we have reviewed and analyzed (1). It appears that synthetic methods of the type D [the reaction of organometallic reagents on carboxylic acid derivatives and in particular with acid chlorides (D_{3a})] are in fact the only methods capable of yielding very hindered ketones. The synthetic conditions, however, remain poorly defined-the reported yields for a given ketone being quite divergent [e.g. In the preparation of hexamethylacetone the yields range from 30% to 88% (2)].

In consideration of the increasing interest in the synthetic possibilities of organocopper reagents [obtained from organomagnesium (2) or organolithium reagents (3)], we deem it timely to publish here some of the observations based on our past and current work, which seeks to determine the effect, origin and use of variation of the principal experimental parameters involved in the condensation :

$$\mathrm{RM} + \mathrm{R'COCl} \xrightarrow{\mathrm{CuX}} \mathrm{RCOR'}$$

The exact choice of experimental conditions is particularly important when the steric hindrance in the reactants exceeds certain limits. In this study we have considered the following :

- Influence of the cuprous halide
- Nature of the organometallic
- Mode of addition of the reagents
- Effect of reaction temperature

In this note we point out that it is possible by a judicious choice of experimental conditions to prepare some hindered aliphatic ketones in satisfactory yields.

Influence and nature of the cuprous halide . - In the case of secondary and tertiary organometallic reagents the presence of a cuprous halide is indispensable for the orientation of the reaction towards ketone formation (2b,4). However with primary organometallics the catalyst is not essential and, if it happens to be cuprous chloride, may lead to competing reactions of a radical nature (5). Cuprous iodide enables one to avoid these competing reactions, resulting in good yields of ketones (Tables I and II).

Comparison of organomagnesium and organolithium reagents-Nature of the alkyl magnesium halides. - In the majority of studies in which this type of reaction has been used, the reagent has been an organomagnesium (2) ; the use of organolithium reagents is quite recent (3). The results presented here show that the latter also leads to ketone formation. In addition to this, the organolithium reagents are not subject to the competing radical reactions which, for organomagnesium reagents, are a function of the nature of the alkylmagnesium halide as well as the cuprous halide (Table II and III).

Mode of addition of the reagents . - The mode of addition of the different reagents is important. One can add the organometallic reagent to a mixture of acid chloride and cuprous halide (mode of addition A). It is also possible to add the acid chloride to a mixture of the organometallic reagent and cuprous halide (mode of addition B). Our results show quite clearly that the mode of addition A is always preferable particularly for organomagnesium reagents different from MeMgX because of the instability of the organocopper intermediate formed (6). (Tables I and II).

Reaction temperature . - Results obtained in this laboratory demonstrate the great sensitivity of the reaction to temperature variation (2a). At -78° the organomagnesium reagents do not react with the acid chloride even in the presence of cuprous chloride (addition A or B). Indeed after stirring the reaction mixture for several hours and hydrolyzing at -78°, there is no observable reaction between EtMgBr and $\underline{i}$-$Pr_2CHCOCl$ (Table II) ; the yield in ketone is 7% for a reaction temperature of -50°. At -5° the radical reaction is very important (5). The most satisfactory way of performing the condensation appears to be combining the reagents at -78° (where no reaction occurs) and permitting the reaction mixture to attain room temperature gradually. The ketone formation takes place slowly during the course of this temperature evolution and no radical reaction occurs. At -78°, organolithium are reactive towards acid chlorides in the presence of cuprous halide. (Tables I and II).

CONDENSATION RLi OR RMgX - R'COCl

Tables	R'COCl	RM [†]	Conditions			Yield in ketone %
			CuX	Temp.	Addition	
I	tBuCOCl	iPrLi	CuI	-78°	A	94
		iPrLi	CuI	-78°	B	67
		tBuMgBr	-	-5°	A	26
		tBuMgBr	CuCl	-5°	A	88
II	iPr$_2$CHCOCl	MeLi	CuI	-78°	A	95
		MeLi	CuCl	-78°	A	72
		EtLi	CuCl	-5°	A	84
		EtLi	CuCl	-5°	B	80
		tBuLi	CuCl	-5°	A	80
		EtMgBr	CuCl	-5°	A	58[††]
		EtMgBr	CuCl	-5°	B	5[††]
		EtMgBr	CuCl	-78°	A	0
		EtMgBr	CuI	-5°	A	97
		tBuMgBr	CuI	-5°	A	86
		Et$_3$CMgCl	CuCl	-5°	A	77
III	iPr$_3$CCOCl	EtMgBr	-	-5°	A	80
		EtMgBr	CuCl	-5°	A	6[††]
		EtMgI	-	-5°	A	33[††]

[†] the organomagnesium reagents have been prepared in ether, the organolithium reagents in ether (MeLi,EtLi) or in pentane (EtLi,iPrLi,tBuLi).

[††] important competing radical reaction.

Conclusion . - The results show the effect of different factors and allow the definition of optimal synthetic conditions whose goals are the following :

a. limitation of reduction by the use of a cuprous halide when the organometallic is sterically hindered.

b. the avoidance of radical reactions in the case of sterically hindered acid chlorides by using RLi or for RMgX by the use of specific experimental conditions.

This synthetic method is very efficient ; it is only limited by the availability of sterically hindered secondary and tertiary halides (7).

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