

IONIC AND RADICAL MECHANISMS IN THE COPPER-CUPROUS CHLORIDE CATALYSED REACTION
OF GRIGNARDS WITH ACID CHLORIDES. SYNTHESIS OF α -DIKETONES AND
HINDERED DI-(sec-ALKYL) KETONES.

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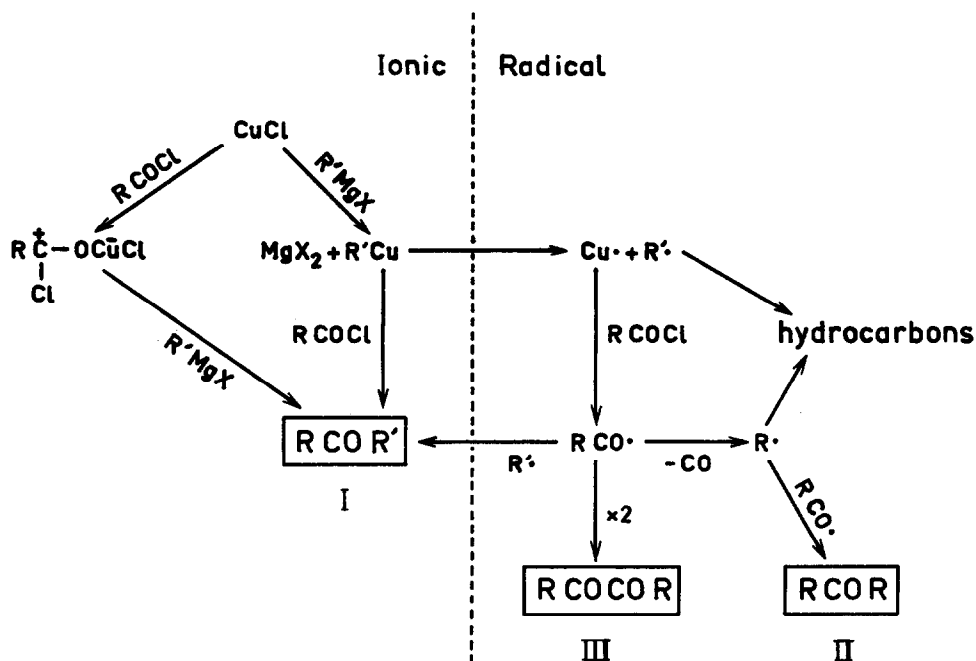
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Two mechanisms for the reaction of a Grignard reagent with an acid chloride in the presence of metallic halides have been proposed. The formation of benzils in the reactions of some benzoyl chlorides led Kharasch (1) to suggest that the catalyst reacted with the Grignard to give an unstable organometallic compound (2) and that a radical mechanism was operative. On the other hand, Percival, Wagner, and Cook (3), working on aliphatic compounds, were unable to detect any disproportionation or coupling products which should result from such a mechanism, and therefore concluded in favour of an ionic mechanism involving the formation of an acid chloride-catalyst complex (4). The reasons for this apparent dichotomy were not discussed.

In previous publications (5), we have reported the synthesis of highly encumbered di-alkyl ketones by this condensation, using, in particular, copper-cuprous chloride catalyst mixtures. Our attempts to synthesize di-(sec-alkyl) ketones, however, have been restricted by the non-availability of the higher sec-alkyl halides. We were led to consider the possibility that the two mechanisms, radical and ionic, were in competition (Schema) and that under certain circumstances the radical mechanism would predominate, thus providing a route to the desired di-(sec-alkyl) ketones (6).

We are now able to report the successful synthesis of two such compounds by the coupling of radicals derived solely from the acid chloride.

Thus, the reaction (7) of ethylmagnesium bromide with di-tert-butylacetyl chloride or with di-isopropylacetyl chloride gave, in addition to the normal product I, the symmetrical ketone II and the symmetrical α -diketone III. This result is in marked contrast to that obtained with the tertiary acid chlorides, as is shown in Table 1. The nature of the Grignard reagent is also of considerable importance : a quite different result would have been observed if $(Et)_3MgBr$, say, had been used (Table 2).



Schema. - Ionic and Radical Mechanisms for the CuCl-catalysed Condensation of RCOCl and R'MgX

Three lines of evidence support the mechanistic schema detailed above :

- (i) Whereas the reaction gives high yields of the normal ketone I when copper alone is used as catalyst, CuCl is essential for the formation of II and III (Table 3),
- (ii) The product composition in the reaction of di-isopropylacetyl chloride with EtMgBr was affected markedly by ultraviolet irradiation (8), but solely when a catalyst was employed : in its absence only the normal ketone was formed (Table 4),
- (iii) The formation of II and III is blocked by the introduction of a suitable radical trap, such as α -methylstyrene.

These results would, therefore, appear to be entirely consistent with the occurrence of the radical mechanism in the reaction of an aliphatic acid chloride with a Grignard reagent. At present, this constitutes the only method for the synthesis of the more ramified symmetrical sec-alkyl ketones. The yield is, however, a sensitive function of the structure of R in RCOCl, insofar as this determines the ease of formation and the stability of the RCO· and R· radicals. It would have been hard to foresee that a relatively small change in the alkyl group, in passing from (t-Bu)₂CHCOCl to (i-Pr)₂CHCOCl, should lead to such a pronounced change in the products. Further studies on the orientation of the reaction as a function of structure and medium are in hand.

Effects of Various Factors on Product Composition in the Reaction of

RCOCl with R'MgBr :

Table 1 : Structure of the acid chloride

Table 2 : Structure of the Grignard reagent

Table 3 : Nature of the catalyst

Table 4 : Ultraviolet irradiation

TABLE	Catalyst	R	R'	% RCOR' I	% RCOR II	% RCOCOR III
1	Cu-CuCl	t-Bu	Et	95	0	0
	Cu-CuCl	t-Bu(Me) ₂ C	Et	95	0	0
	Cu-CuCl	(i-Pr) ₂ CH	Et	60	2	20
	Cu-CuCl	(t-Bu) ₂ CH	Et	41	41	10
2	Cu-CuCl	(i-Pr) ₂ CH	Et	60	2	20
	Cu-CuCl	(i-Pr) ₂ CH	t-Bu	86	1	5
	Cu-CuCl	(i-Pr) ₂ CH	(Et) ₃ C	77	0	0
3	Cu	(t-Bu) ₂ CH	Et	95	traces	traces
	CuCl	(t-Bu) ₂ CH	Et	50	37	13
	Cu-CuCl	(t-Bu) ₂ CH	Et	41	41	10
4	none	(i-Pr) ₂ CH	Et	80	0	0
	hv only	(i-Pr) ₂ CH	Et	83	0	0
	Cu-CuCl	(i-Pr) ₂ CH	Et	60	2	20
	Cu-CuCl/hv	(i-Pr) ₂ CH	Et	30	4	38

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- (3) W.C. Percival, R.B. Wagner and N.C. Cook, J.Amer.Chem.Soc., 75, 3731 (1953).
- (4) Various structures have been advanced for acid chloride-metal halide complexes : see J.Michel, E. Henry-Basch and P. Fréon, Bull.Soc.chim., Fr., 4898 (1968).
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J.E. Dubois, B. Leheup, F. Hennequin and P. Bauer, Bull.Soc.chim.,Fr., 1150 (1967).
- (6) An unstable organo-copper compound appears to be formed when a cuprous halide reacts with a Grignard : H. Gilman, R.G. Jones and L.A. Woods, J.Org.Chem., 17, 1630 (1952).
- (7) All reactions were carried out under strictly standardized conditions. To 0.02 mole of catalyst (0.02 mole Cu + 0.02 mole CuCl) in ether (15 ml) at 0° was added 0.02 mole of the acid chloride in ether (15 ml) over a period of 10 min., followed by EtMgBr (0.025 mole ; 1 N in ether) over a period of 90 min. . After the addition, the mixture was stirred at 0° for a further 30 min. and at room temperature for 90 min. . Product yields were determined by glpc. The products were isolated by preparative glpc, and characterized by carbon-hydrogen analysis, nmr, ir, uv, and mass spectroscopy.
- (8) Irradiation experiments were conducted in quartz apparatus ; a Philips type HP 120 lamp with peak emission at 254 mμ was used.