Grignard Reagent–Acid Chloride Condensation in the Presence of Copper(I) Chloride. A Study of Structural Effects by Direct and Competition Methods

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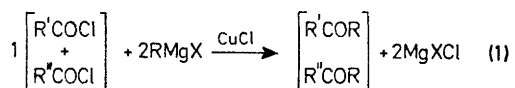
The copper(I) chloride catalysed reaction between a Grignard reagent and an acid chloride in ether has been studied by using a competition method in which a pair of acid chlorides reacts with a single Grignard reagent, and by direct kinetic experiments in one case. The variation of relative rates produced by structural changes in the alkyl group of the acid chloride has been shown to correlate with the Taft polar parameter σ^* but to be independent of the steric parameter E_S ($\rho^* = 2\cdot96$ for EtMgBr; $6\cdot01$ for Bu^{t}CH$_2$MgCl; $12\cdot7$ for Bu^{t}MgCl); this is in contrast with uncatalysed reactions of this type which have a marked sensitivity to steric effects. These results are consistent with a cyclic transition state in which chloride is displaced from acid chloride without addition to the carbonyl group, by either a mixed cuprate(I) intermediate [RCuX]$^-$MgX$^+$ or a loose RCu $\cdots$ MgX$_2$ complex.

WE have been interested for some time in the synthesis and spectroscopic properties [1a–c] of highly hindered ketones. Most of the available synthetic methods [2] have rather severe steric requirements and are not therefore of general utility: the most promising method appears to be the copper(I) chloride catalysed condensation of a Grignard reagent with an acid chloride. We have attempted to optimise the yields in this reaction by varying the catalyst, solvent, temperature, and order of combining reagents,[3] and have been able to synthesise the ketone Bu^{t}Me$_2$C·CO·CMe$_2$Bu^t in 70% yield.[4]

The fact that such a bulky ketone (Bu^{t}Me$_2$C E_S, $-3\cdot9$) can be prepared in good yield causes speculation concerning the reaction mechanism: we now examine the system in a more quantitative manner in order to shed light on the mechanism and scope of this reaction.

The reaction system, unfortunately, is heterogeneous. We have previously described [5] competition experiments in which a pair of acid chlorides reacted with a single Grignard in the presence of catalyst, thereby circumventing this difficulty. We now report results of competition experiments on several related systems, to demonstrate the generality of our previous results, and of direct kinetic experiments on a system particularly amenable to such a study, viz. the catalysed reaction of neopentylmagnesium chloride with acid chlorides.

The competition experiments involved slow addition of a Grignard reagent to a mixture of acid chlorides in ether [equation (1)]. The copper(I) chloride acts as a catalyst

$$1\begin{bmatrix} R'COCl \\ + \\ R''COCl \end{bmatrix} + 2RMgX \xrightarrow{\text{CuCl}} \begin{bmatrix} R'COR \\ R''COR \end{bmatrix} + 2MgXCl \quad (1)$$

by reacting with the Grignard reagent to form an organo-copper intermediate which in turn reacts with acid chloride, to yield ketone and regenerate the copper(I) chloride. The relative reactivities of the acid chlorides are calculated from the ratio of ketones obtained (under our conditions these are the only products).

The direct experiments were carried out by addition of neopentylmagnesium chloride to copper(I) chloride in ether at $-5\ ^\circ$C; an organocopper intermediate which can persist for several hours without decomposition is formed. After the addition of acid chloride the condensation was studied by the removal of aliquot portions at intervals, and quenching and analysing these by g.l.c.

Only non-reducing organocopper reagents (e.g. methyl, neopentyl, benzyl) appear to have sufficient thermal stability for such a study.[6] The organocopper reagent thus formed is not completely soluble in ether; its solubility under our experimental conditions has been determined (cf. Experimental section). Its rate of dissolution appears to be sufficiently rapid with respect to the rate of its reaction with acid chloride such that the organocopper concentration remains essentially constant throughout the reaction. This is supported by the observation that the reaction is first order with respect to acid chloride.

RESULTS AND DISCUSSION

Table 1 gives the results for reactions between various pairs of acid chlorides and EtMgBr, Bu^{t}CH$_2$MgCl, and Bu^{t}MgCl, respectively, in the presence of copper(I) chloride at $-50\ ^\circ$C. In each series one member of the acid chloride pair was held constant so as to calculate the relative reactivities with respect to the same reference. The reference acid chloride for Series I was propionyl and for Series II and III pivaloyl. The latter choice was made to ensure greater precision in the ensemble of relative reactivities, since the reactivity spread is greater for these Series than for Series I.

The rate constants for the reaction of the organocopper reagent derived from neopentylmagnesium chloride and copper(I) chloride, with various acid chlorides are shown in Table 2. These are given as pseudo-first-order rate constants; the reaction order with respect to the organocopper intermediate is unknown since it was not possible to alter this concentration without using rather dilute

[1] (a) J. E. Dubois and A. Massat, Chem. Comm., 1968, 778; (b) J. E. Dubois, A. Massat, and P. Guillaume, J. Chim. phys., 1968, 65, 729; (c) J. E. Dubois and A. Cossé-Barbi, Spectrochim. Acta, 1972, 28A, 523, 539, 561.

[2] J. E. Dubois, F. Hennequin, and M. Boussu, Bull. Soc. chim. France, 1969, 3615.

[3] J. E. Dubois and M. Boussu, Tetrahedron, 1973, 29, 3943.

[4] J. E. Dubois and M. Boussu, unpublished data.

[5] J. A. MacPhee and J. E. Dubois, Tetrahedron Letters, 1972, 467.

[6] M. Tamura and J. Kochi, J. Organometallic Chem., 1972, 42, 205.

solutions. The validity of these rate constants rests on two assumptions: (a) that the acid chloride reacts much more rapidly with the organocopper reagent in solution than with the solid phase; and (b) that the rate of dissolution of the organocopper reagent is much faster than

TABLE 1

Relative reactivities of acid chlorides (RCOCl) towards various Grignard reagents in the presence of copper(I) chloride by competition experiments (T $-50°$)

			k_R/k_o		
			Series I	Series II	Series III
R	σ^*	E_S	EtMgBr	Bu^tCH_2Cl	Bu^tMgCl
Et	-0.100	-0.07	1.00 *	28.2	
Pr^n	-0.115	-0.37	1.00		
Pr^i	-0.190	-0.47	0.521	3.06	
Bu^i	-0.125	-0.93	0.840	24.2	90.1
Bu^t	-0.300	-1.54	0.248	1.00 *	1.00 *
Bu^tCH_2	-0.165	-1.74	0.626	5.40	59.2
Et_2CH	-0.225	-1.98	0.558	2.60	5.59
Et_3C	-0.340	-3.8		0.826	0.264
Pr^i_2CH	-0.260		0.137	0.662	1.38
Bu^tMe_2C	-0.345	-3.9		0.413	

* By definition.

TABLE 2

Pseudo-first-order rate constants for the reaction of acid chlorides (RCOCl) with the neopentylcopper reagent (T $-5°$)

R	σ^*	$10^3k/s^{-1}$
Bu^tCH_2	-0.165	92
Et_2CH	-0.225	15.1
Bu^t	-0.300	10
Bu^tMe_2C	-0.345	6.7
Pr^iMe_2C	-0.330	3.0
Pr^i_2CH	-0.260	1.7
Pr^i_3C	-0.390	0.62
Bu^t_2CH	-0.290	0.14

its reaction with acid chloride, so that the concentration of the former remains constant during the reaction. The first assumption is reasonable; solute–solid reactions are in general much slower than solute–solute reactions, owing to concentration and contact area effects. The second is supported by the fact that the reaction is first order in acid chloride. If the concentration of organo-copper reagent in solution were significantly altered by reaction, the rate determining step would be its rate of dissolution (especially for the more reactive acid chlorides) and the rate constant would be independent of acid chloride concentration, i.e. zero order. This is contrary to observation.

Substituent Effects.—The results of both direct and competitive experiments are considered in terms of the Taft parameters [7] E_S and σ^*. Figures 1—3 demonstrate that the relative reactivities determined from the competitive experiments are correlated in a reasonable manner by the Taft σ^* value. The line A in Figure 4 shows that a correlation of the same type exists for the directly measured rate constants, although it is less satisfactory.

With correlations of this kind, which involve only alkyl

[7] R. W. Taft, jun., in ' Steric Effects in Organic Chemistry,' ed. M. S. Newman, John Wiley, New York, 1956, p. 556.

groups, Koppel [8a] and Tuulmets [8b] have noted that for a series of alkyl groups bearing the same number of α hydrogens there is an intrinsic correlation between σ^*
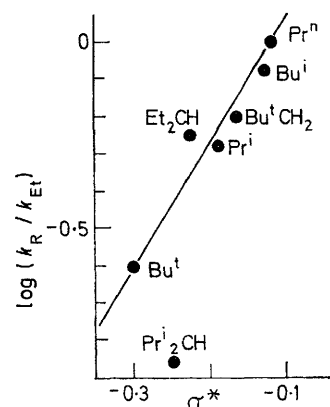

FIGURE 1 Competition experiments. Reaction of EtMgBr with acid chlorides, CuCl catalyst ($\rho^* = 2.96 \pm 0.38$, $r_d^i = 0.97$)
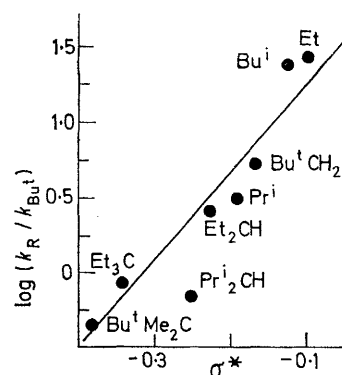

FIGURE 2 Competition experiments. Reaction of Bu^tCH_2MgCl with acid chlorides, CuCl catalyst ($\rho^* = 6.01$, $r = 0.97$)
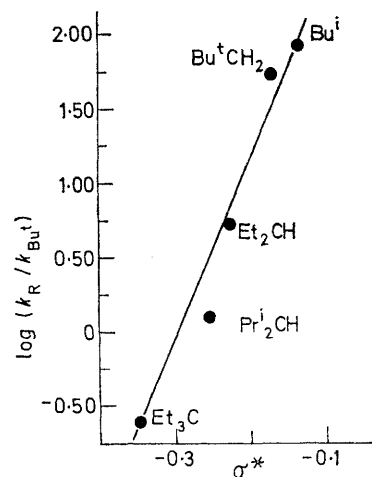

FIGURE 3 Competition experiments. Reaction of Bu^tMgCl with acid chlorides, CuCl catalyst ($\rho^* = 12.7 \pm 0.14$, $r = 0.97$)

and E_S. In such a case data might be found to correlate with a linear combination of these parameters or with

[8] (a) I. A. Koppel, *Reakts. spos. org. Soedinenii*, 1965, **2** (2), 26 (in Russian) (*Chem. Abs.*, 1966, **64**, 571); (b) A. Tuulmets, *ibid.*, 1967, **4** (1), 17 (in Russian) (*Chem. Abs.*, 1968, **69**, 43,202).

either parameter taken separately, and the result would be without significance. This difficulty is obviated in the present case by a sufficiently varied choice of alkyl group.

The relative rates measured in Series I—III were subjected to the four-parameter version of the Taft equation [$\log (k/k_R) = \rho^*\sigma^* + \delta E_S$] to determine whether the steric effect is of importance. The correlation yields essentially the same value of ρ^* as that obtained from the two-parameter equation with δ ca. 0. This demonstrates
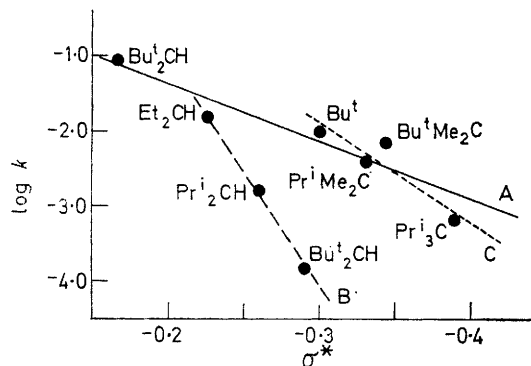

FIGURE 4 Direct kinetic experiments. Reaction of the neopentylcopper reagent with acid chlorides (solid line A, $\rho^* = 8\cdot0$; dotted line C, $\rho^* = 12\cdot9$; dashed line B, $\rho^* = 31\cdot1$). For explanation of lines see text

unambiguously the unimportance of steric effects for this reaction. Series IV (Figure 4) involves direct kinetic measurements of the reaction system used in Series II, but carried out at -5 rather than -50 °C. Series IV contains rate measurements for some rather sterically hindered acid chlorides, viz. $Pr^i_2CHCOCl$, Bu^tMe_2CCOCl, Pr^iMe_2CCOCl, $Bu^t_2CHCOCl$, and Pr^i_3CCOCl. With the exception of two acid chlorides bearing hindered secondary alkyl groups, viz. $Bu^t_2CHCOCl$ and $Pr^i_2CHCOCl$, the points fall on the solid line in Figure 4. The ρ value corresponding to this line (8·0) is not significantly different from that determined for Series II (6·01). It should also be noted that for Series I—III the point corresponding to $Pr^i_2CHCOCl$ falls below the correlation in each case (see Figures 1—3).

The correlation in Figure 4 is not as satisfactory as those obtained for the other three Series where it was possible to demonstrate the lack of dependence of reactivity on steric effects. Unfortunately steric constants are available only for four of the groups used in Series IV (Bu^tCH_2, Et_2CH, Bu^t, and Bu^tMe_2C) so that this question cannot be completely answered. A correlation of the data corresponding to these four points in terms of E_S and σ^* yields a ρ^* value of 6·4 and a δ of $-0·05$, essentially the same as obtained for Series II. Thus the results for the direct kinetic experiments allow

the same general conclusion concerning the unimportance of steric effects as the competitive experiments.

An alternative analysis of these data is apparent from Figure 4: two correlation lines may be drawn—one for secondary (B) and the other for tertiary (C) alkyl groups. This is an attractive observation but we feel that it is fortuitous for two reasons: first the unprecedented, anomalously large slope (ρ^* 31·1) for secondary alkyl groups; and secondly the dependence of the ρ^* values measured in Series I—III to changes in Grignard structure. This second point merits clarification. If the dispersion observed in Figure 4 is 'real,' the correlation lines shown in Figures 1—3 are meaningless and result simply from the limited number of compounds used. However, as is shown in Figure 5, the ρ^* value determined in this way appears to be a linear function of the σ^* value of the alkyl group of the Grignard reagent. It is difficult to reconcile this behaviour with the arbitrary slopes obtained because of a dearth of points. It would therefore appear that the dispersion observed is not 'real' and that the points corresponding to Pr^i_2CH and Bu^t_2CH, both rather hindered secondary groups, do not correlate for reasons as yet unknown.

The correlation shown in Figure 5 is in the sense anticipated—i.e. the more electron-donating the alkyl group of the Grignard reagent, the greater the sensitivity of the reaction to change in the alkyl group of the acid chloride —but the linearity observed is somewhat surprising.

Thus it appears that the reaction under consideration is, quite generally, controlled by the polar effect, with the steric effect relatively insignificant.
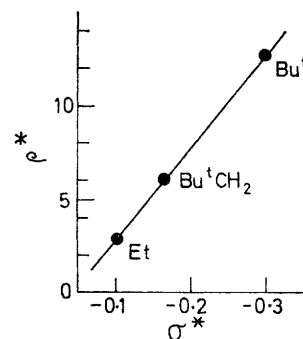

FIGURE 5 Sensitivity of the polar reaction constant to changes in Grignard reagent

Related Systems.—The observation that the copper(I) chloride catalysed condensation of Grignard reagents with acid chlorides is controlled by polar effects is of prime mechanistic importance when one considers analogous systems. Reactions involving addition to or displacement at the carbonyl group are generally markedly sensitive to steric effects. The present case constitutes an exception to the general behaviour. For example, the rates of addition of ethylmagnesium bromide to a series of dialkyl ketones [9] correlate with the steric parameter E_S^0 † ($\delta = 1·87$, $r = 0·976$); the rates

† The parameter E_S^0 is a steric parameter related to E_S by the relationship $E_S^0 = E_S - 0·2(3 - n_H)$, where n_H is the number of α-hydrogens. This parameter, developed by Pal'm, gives in general a slightly better correlation than E_S. It is discussed in detail in 'Fundamentals of the Quantitative Theory of Organic Chemistry,' V. A. Pal'm, Leningrad, 1967, ch. 10. See also, J. Shorter, in 'Advances in Linear Free Energy Relationships,' eds. N. B. Chapman and J. Shorter, Plenum Press, London, 1972, p. 95.

[9] J. Vaiga, M. Luuk, and A. Tuulmets, Reakts. spos. org. Soedinenii, 1971, 8 (1), 27 (in Russian) (Chem. Abs., 1972, 76, 3043).

of addition of a series of alkylmagnesium bromides to pinacolone [8b] correlate with a linear combination of E_S^0 and σ^* ($\rho^* = -3.1$, $\delta = 1.92$, $r = 0.990$); the acid catalysed methanolysis of β-naphthyl esters [10] correlates uniquely with E_S while the base catalysed methanolysis of 1-menthyl esters [11] correlates with a linear combination of E_S and σ^*. These reactions are all considered to pass through a transition state involving addition to the carbonyl group. The present results, which do not depend on steric effects, suggest a difference in mechanism between the Grignard reagent–acid chloride condensation and the systems cited above.

Addition of Organocopper Reagents to Ketones.—Data for the addition of a Grignard reagent to ketones under the same catalytic conditions as served for the acid chloride reaction are of great interest; these could indicate the response of the addition of an organocopper species to structural changes in the ketone. Cuprates prepared from organolithium reagents are extremely unreactive towards the carbonyl group: [12] it is possible, for example, to replace the halogen of an α-halogenoketone by an alkyl group using a reagent of this type without concomitant addition to the carbonyl group.[13] Rather surprisingly, however, it has recently been demonstrated that organocopper species derived from Grignard reagents *do* add to carbonyl groups under conditions in which the corresponding lithium cuprates are unreactive.[4] This makes it possible to determine the relative reactivities of a series of ketones CH$_3$COR with EtMgBr catalysed by copper(I) chloride. The results in Table 3 correlate with

TABLE 3

Relative reactivities of ketones (RCOMe) towards ethylmagnesium bromide catalysed by copper(I) chloride (T $-5°$)

R	k_R/k_{Pr^i}	E_S^0
Et	1.84	-0.27
Pr^i	1.00	-0.87
Bu^i	0.892	-1.13
Bu^{t}CH$_2$	0.128	-1.94
Bu^t	0.101	-2.14

E_S^0 alone, as was found by Tuulmets for the uncatalysed addition,[9] but with a smaller constant of proportionality (δ 0.71) than in the latter case (δ 1.87). This, then, is direct evidence to support the conclusion that the lack of dependence of reaction (1) on steric effects is mechanistically significant.

Mechanistic Inferences.—The reaction between a copper(I) salt and a Grignard reagent has been described as involving cuprates,[14] both symmetrical (I) and mixed

$$[RCuR]^-MgX^+ \qquad [RCuX]^-MgX^+$$
$$(I) \qquad\qquad (II)$$
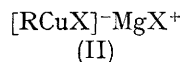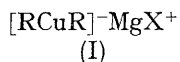
(II), by analogy with previous work on lithium cuprates [15] and also in terms of more recent evidence. Others [16]

discuss organocopper species RCu. The present experimental conditions—addition of a dilute Grignard reagent in ether to an ethereal solution of the acid chloride containing the copper(I) chloride—stoicheiometrically allow formation of a mixed cuprate, but a symmetric cuprate is unlikely. The reaction of the Grignard with the cuprous chloride can be represented as in equation (2),
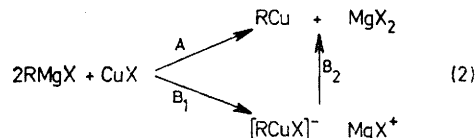
where the RCu species can be formed directly or *via* the mixed cuprate. The lack of dependence on steric effects of reaction (1) suggests that the transition state differs fundamentally from those of the systems discussed above. Two points upon which this difference might be based are (i) the absence of direct attack on the carbonyl group, and (ii) a relatively open transition state. The first might be expressed more explicitly in terms of a nucleophilic displacement of chloride by the organocopper intermediate; the second by a cyclic transition state.

Tuulmets has studied the reaction of a series of alkylmagnesium bromides with pinacolone [8b] and was able to separate the rates of addition, reduction, and enolization. He correlated the rate data with ρ^* and E_S^0 and found the following: (i) reduction correlates with σ^* alone (ρ^* -0.58); (ii) addition correlates with σ^* and E_S^0, with E_S^0 predominating ($\rho^* = -3.1$, $\delta = 1.92$); (iii) enolization correlates with σ^* and E_S^0, with σ^* predominating ($\rho^* = -15.8$, $\delta = 1.0$). These results are rationalized by Tuulmets in terms of the transition states (III)—(V),

(III) Reduction   (IV) Addition   (V) Enolization
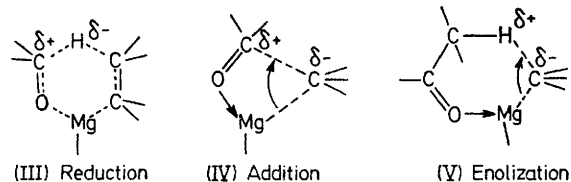
where the four-centre transition state is strongly influenced by steric effects and the six-centre but slightly, or not at all.

With these ideas in mind we may enquire which is the more likely form of the organocopper intermediate (RCu or [RCuX]$^-$MgX$^+$), in terms of the transition state it is capable of producing. A mechanism (VI) involving the

(VI)   (VII)

[10] W. Hafenist and R. Baltzly, *J. Amer. Chem. Soc.*, 1947, **69**, 326.

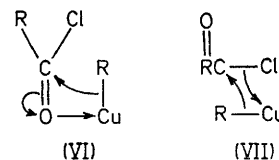[11] W. S. Pavelich and R. W. Taft, jun., *J. Amer. Chem. Soc.*, 1957, **79**, 4935.

[12] G. H. Posner, C. E. Whitten, and P. E. McFarland, *J. Amer. Chem. Soc.*, 1972, **94**, 5106.

[13] G. H. Posner and J. J. Sterling, *J. Amer. Chem. Soc.*, 1973, **95**, 3076.

[14] N. T. Luong-Thi and H. Rivière, *Tetrahedron Letters*, 1971, 587.

[15] N. T. Luong-Thi and H. Rivière, *Tetrahedron Letters*, 1970, 1579, 1583.

[16] M. Tamura and J. K. Kochi, *J. Amer. Chem. Soc.*, 1971, **93**, 1485.

species RCu, and a simple metathetical displacement of chloride (VII) are unlikely since both require a four-centre transition state and would consequently be sensitive to steric effects.

On the other hand, a mixed cuprate could react *via* a six-centre transition state, (i) by addition to the carbonyl (VIII), or (ii) by displacement of chloride ion (IX).

(VIII)

(IX)
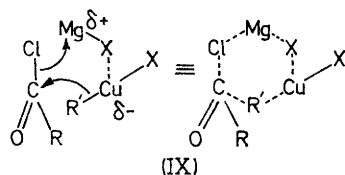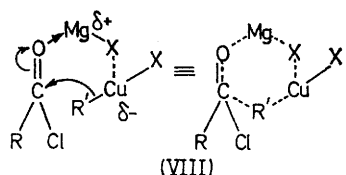
An alternative to the mixed cuprate intermediate is a loose complex between RCu and MgX_2. This might be formed by reaction between the Grignard reagent and the copper(I) chloride and be held in a solvent cage long enough to react as a unit with acid chloride. Thus, MgX_2 could act as a catalyst permitting RCu to circumvent steric effects by passage through a six-centre transition state, such as (X) or (XI). In view of the experimental conditions (slow addition of Grignard reagent to an excess of catalyst and acid chloride in ether), it is rather unlikely that a species RCu formed by step A or

(X)   (XI)   (XII)
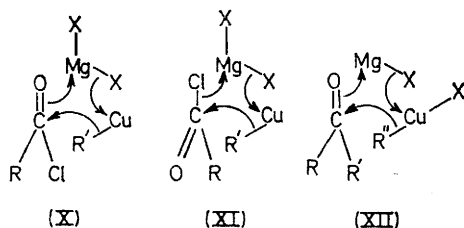
steps B_1 and B_2 [equation (2)] would encounter MgX_2 to act as catalyst. The acid chloride concentration is much larger than that of MgX_2 so that any RCu formed would tend to encounter the former rather than the latter. This implies, in effect, that the difference between a mixed cuprate and a loose complex becomes very subtle indeed —both are capable of being formed by the same reaction step and both lead to a similar transition state by reaction with acid chloride.

The copper(I) chloride catalysed addition of ethylmagnesium bromide to aliphatic ketones correlates with E_s^0 but with a constant of proportionality (δ 0·71) smaller than in the case of the uncatalysed addition (δ 1·87).

This more feeble dependence on the steric effect for the catalysed reaction might be due to passage *via* a six-centre transition state (XII). Thus the reaction involving acid chloride, for which there is no dependence on the steric effect, probably passes through a transition state resembling (IX) or (XI) which are virtually indistinguishable, in which halogen is displaced from the acid chloride with no change of hybridization at the carbonyl carbon.

Role of the Carbonyl Group.—The carbonyl group strongly activates the reaction of acid chlorides with organocopper reagents. These reagents also react with alkyl halides to replace the halogen by an alkyl group and with α-halogeno-acid chlorides to yield exclusively α-halogeno-ketones.[17] Thus whether or not the carbonyl group participates in the reaction by a change of hybridization in the transition state from sp^2 to sp^3, it is, nevertheless, responsible for the high reactivity of acid chlorides in this reaction. This can be explained by the polarization of the carbonyl group, which facilitates nucleophilic attack on the carbonyl carbon. The importance of the polarization is reflected in the high sensitivity of the reaction to changes in the acid chloride, especially when the Grignard reagent is t-butylmagnesium chloride (ρ^* 12·7). Such a marked dependence on σ^* is usually considered to be indicative of a high degree of charge separation in the transition state.

EXPERIMENTAL

The reaction conditions for the competition experiments have been described previously.[5] The reaction products were analysed by g.l.c. (Girdel apparatus equipped with flame ionization detector) using a column of SE-30 10% on Chromosorb W. The identity of the products was checked by comparison with authentic samples. The relative reactivities given in Table 1 were determined from the relative amounts of ketones formed in each experiment. The reproducibility of the ketone concentrations was ±3% or better.

Materials.—*Copper*(I) *chloride.* Prolabo analytical grade product (pale green) was purified according to Vogel's method.[18] This white powder was stored in a dry box under a nitrogen atmosphere prior to use.

Diethyl ether. Prolabo ether was dried ($CaCl_2$), filtered, and distilled from NaH or $LiAlH_4$ onto sodium wire.

Carboxylic acids. The carboxylic acids were commercial samples (except as mentioned below) and were used without further purification in the preparation of the acid chlorides.

2,2-Diethylbutyric acid was obtained by carboxylation of the Grignard reagent using CO_2 gas under pressure: the chloride for the Grignard was obtained from 1,1-diethylpropan-1-ol as previously described.[19] 2,2,3,3-Tetramethylbutyric acid was obtained as for 2,2-diethylbutyric acid. 2-Isopropyl-3-methylbutyric acid was prepared following the procedure given by Newman.[20]

Acid chlorides. Propionyl and pivaloyl chlorides were commercially obtained (Prosynor). The other acid chlorides were prepared from the corresponding carboxylic acid using

[17] N. T. Luong-Thi, H. Rivière, and A. Spassky, *Bull. Soc. chim. France*, 1973, 2102.

[18] A. I. Vogel, 'A Textbook of Practical Organic Chemistry,' 3rd edn., Longmans, Green and Co., London, 1956.

[19] J. E. Dubois, M. Chastrette, and E. Schunk, *Bull. Soc. chim. France*, 1967, 2010.

[20] M. S. Newman and T. Fukunaga, *J. Amer. Chem. Soc.*, 1963, **85**, 1176.

the thionyl chloride procedure of Vogel.[18]   The acid chlorides were purified by distillation with the exception of 2,2,3,3-tetramethylbutanoyl chloride (Bu^{t}Me$_2$CCOCl, m.p. 73°) which was purified by sublimation.

Magnesium.   The magnesium was obtained from the Société du Magnesium (France) as sublimed grade containing not more than 300 p.p.m. of metallic impurities.

Alkyl halides.   Ethyl bromide, neopentyl chloride, and t-butyl chloride were obtained commercially (Rhône–Poulenc); before use they were distilled and stored over anhydrous K$_2$CO$_3$.

Ketones.   The ketones whose reactivity is reported in Table 3 were obtained commercially (Prosynor, Fluka). Their purity was checked by g.l.c. before use and those products of insufficient purity were redistilled.

Concentration of the Dissolved Organocopper Reagent.—To a stirred suspension of CuCl in ether at —5° a stoicheiometric amount of neopentylmagnesium chloride was slowly added. After complete addition the solution was stirred for 10 min and the solid allowed to settle.   At this point a negative Gilman test showed that no Grignard reagent remained in the solution.   A known volume of the supernatant liquid was removed and added to a known excess of acid chloride in the presence of an internal standard.   The quantity of ketone produced after reaction with the organocopper reagent was determined by g.l.c. and the concentration of organocopper reagent in solution deduced (the neopentyl-copper reagent is soluble to the extent of 0·05M in ether at —5°).

Direct Kinetic Measurements.—To a glass cell thermo-statted at —5° containing ether (35 cm³) and CuCl (5·5 mmol) a solution of neopentylmagnesium chloride (5 cm³; 1·0N) was slowly added.   Upon complete addition of the Grignard reagent the mixture was stirred for 10 min and a stoicheio-metric amount of acid chloride in ether added.   Aliquot portions were removed at intervals, quenched by addition to dilute sulphuric acid, and the amount of ketone formed was measured by g.l.c. relative to an internal standard.   The rate constants determined in this way are pseudo-first-order. The reaction system was at all times protected by a stream of dry argon.