Tetrahedron Letters No. 6, pp 467 - 470, 1972. Pergamon Press. Printed in Great Britain.

KETONE SYNTHESIS VIA THE GRIGNARD REAGENT - ACID CHLORIDE CONDENSATION AS CATALYSED BY CUPROUS CHLORIDE. AN INTERESTING STRUCTURAL REQUIREMENT

John Anthony MacPhee and Jacques-Emile Dubois
(Laboratoire de Chimie Organique Physique de l'Université de PARIS VII,
Associé au C.N.R.S., 1, rue Guy de la Brosse, 75- PARIS 5° - France).

(Received in UK 5 January 1972; accepted for publication 6 January 1972)

Our interest in the synthesis of highly hindered ketones has prompted us to codify and evaluate the available synthetic methods (1). As a result of this bibliographical synopsis we have opted in favour of a promising reaction which has been known for some time (2), viz. the condensation of an acid chloride and a Grignard reagent catalysed by cuprous chloride. We would like at this time to present the results of a study of reactivity using a competition method which reveals some interesting structural requirements of this reaction.

Because the heterogeneous nature of the reaction precludes a conventional kinetic study, we have turned to a competition method in which a pair of acid chlorides is reacted with a single Grignard reagent. The overall reaction may be represented by Equation I.

$$\text{I.} \qquad \left\{\begin{matrix} R'COCl \\ \\ R''COCl \end{matrix}\right\} + RMgCl \xrightarrow{CuCl} \left\{\begin{matrix} R'COR \\ \\ R''COR \end{matrix}\right\} + MgCl_2$$

Current thinking on the mechanism of this reaction (3) centres around the preliminary formation of an organo-copper species by a reaction between Grignard reagent and cuprous halide. This intermediate then reacts with acid chloride yielding ultimately a ketonic product. For the particular case described by Equation I, a rate ratio can be obtained from an analysis of the relative amounts of ketone formed, by assuming that the reaction with respect to acid chloride is first order. The reaction order with respect to intermediate is unimportant since it is common to both acid chlorides (4).

TABLE I

Reactivity of Acid Chlorides Relative to Pivalyl Chloride

R	σ^*	E_s	$k_R/k_{t\text{-}Bu}$
Et	-0.100	-0.07	28.2
i-Pr	-0.190	-0.47	3.06
i-Bu	-0.125	-0.93	24.2
t-Bu	-0.300	-1.54	1.00 [b]
neo-C_5H_{11}	-0.165	-1.74	5.40
$(Et)_2CH$	-0.225	-1.98	2.60
$(Et)_3C$	-0.340 [a]	-3.8	0.826
$(i\text{-}Pr)_2CH$	-0.250 [a]	-	0.662
t-BuMe$_2$C	-0.380 [a]	-3.9	0.413

a $\Sigma\sigma^*$
b by definition

The results given in Table I show how the reactivity of a series of acid chlorides with respect to pivalyl chloride varies when the Grignard is neopentylmagnesium chloride. These data were treated by the four parameter version of the Taft equation (5) (log $(k/k_R = \rho^*\sigma^* + \delta E_S)$ demonstrating that the change in relative reactivity with changing alkyl substituent is successfully correlated by means of the Taft σ^* alone. This is shown by the plot given in Figure 1 where it can be seen that a reasonable straight line is traced out by all points except that corresponding to the group $(i\text{-}Pr)_2CH$.

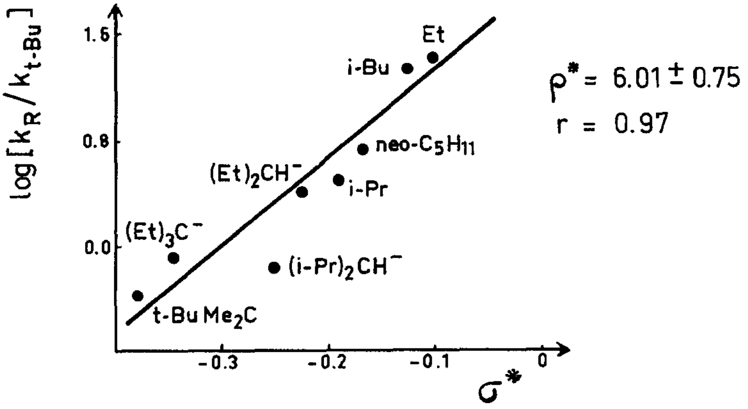


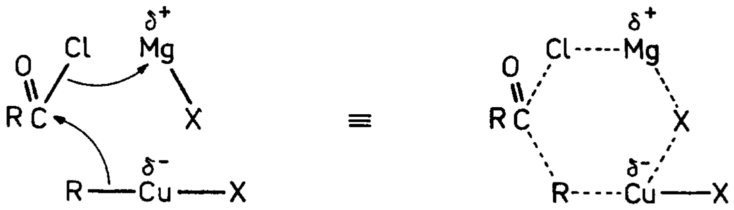
Figure 1.- Correlation of Relative Reactivity with the Taft σ^* .

That a correlation in terms of σ^* is noteworthy may be seen by examining reactions which resemble at least formally the present case and whose mechanistic details are to some extent known. The trans-esterification reaction, involving as it does the displacement of a group -OR by another such group of differing structure, provides a formal analogy. The rates of acid-catalysed methanolysis of β-naphthyl esters (6) has been shown to correlate with E_s ($\delta = 1.38$), while the rates of base-catalysed methanolysis of ℓ-menthyl esters (7) correlate with a linear combination of σ^* and E_S ($\rho^* = 2.7$, $\delta = 1.3$). A recent study by Vaiga et al of the rates of addition of ethylmagnesium bromide to a series of alkylmethyl ketones (8a) is relevant as well. These authors find that the rates are correlated entirely in terms of E_S° ($\delta = 1.87$) (8b). So the reaction under investigation here and those cited for purpose of analogy, in spite of the formal similarity uniting them, i.e. reaction <u>at</u> the carbonyl group, have quite different requirements when viewed in terms of Taft's polar and steric parameters. The trans-esterification reaction, as well as the Grignard addition reaction are believed to take place via transition states involving addition <u>to</u> the carbonyl group (6,7,8a). The fact that the relative rates reported here do not exhibit a steric effect, in contrast to these other reactions, suggests a mechanistic difference. A mechanism in which the halogen of the acid chloride is displaced by the organo-copper intermediate is a reasonable alternative. A conception of the transition state of this reaction depends on a knowledge of the structure of the organo-copper intermediate. The results of recent studies (3) tend to favour this entity as a mixed cuprate I or a symmetric cuprate II.

$$[\mathrm{RCu\,X}]^-\,\mathrm{MgX}^+ \qquad\qquad [\mathrm{RCu\,R}]^-\,\mathrm{MgX}^+$$

X = Halogen

Accepting this, our experimental conditions would favour the formation of I rather than II since the reaction was carried out by slow addition of Grignard reagent to a mixture of acid chlorides and <u>excess</u> CuCl in ether. Formation of II requires excess Grignard reagent. Thus a reasonable picture of the transition state would be III.



in which the R group is added to the acid chloride and the halogen removed in a concerted manner with no substantial interference with the integrity of the carbonyl group.

From the point of view of synthesis the absence of a dependence on E_S in the correlation presented here, as well as the dependence on σ^*, involve a consequence of some importance. Since the range of σ^* values for alkyl groups is quite limited, even for bulky groups, the result implies that this method should be applicable to the synthesis of very hindered ketones in reasonable yields. A recent paper from this laboratory (9) discussed the optimum experimental conditions for this reaction which has since permitted a synthesis of the highly hindered di-triptylketone $(t\text{-BuMe}_2C)_2CO$ in 70% yield. (10).

The sensitivity of this reaction to changes in Grignard structure is an important consideration which we are currently investigating.

REFERENCES

(1) J.E. Dubois, F. Hennequin and M. Boussu, Bull.Soc.Chim.France, 3615 (1969).

(2) W.C. Percival, R.B. Wagner and N.C. Cook, J.Amer.Chem.Soc., **75**, 3731 (1953).

(3) N.T. LongThi and H. Rivière, Tetrahedron Letters, 587 (1971).

(4) The reactions were carried out in a glass cell fitted with a cooling jacket through which methanol at -50° circulated from a cryostat. Standard reaction conditions involved a preliminary mixing of the acid chlorides (0.01 moles of each) with CuCl (0.02 mole) in ether (30 ml), followed by cooling with magnetic stirring. To this mixture was added slowly (∿ 2 hours) a dilute solution of Grignard reagent in ether (0.002 moles in 20 ml ether). After stirring at controlled temperature for two hours the temperature was allowed to rise to room temperature whereupon hydrolysis was effected with 5 ml of 1M H_2SO_4. After hydrolysis the H_2SO_4 was neutralised with excess solid K_2CO_3, to remove the organic acids, and the ketones in the ethereal layer were analysed by vpc. During each run the system was protected by dry argon gas. Each run was done in triplicate. The reproducibility of the ketone percentage was ± 3% or better under our conditions.

(5) R.W. Taft, Jr., in Steric Effects in Organic Chemistry, ed.M.S. Newman, J. Wiley, New York (1956).

(6) W. Hafenist and R. Baltzly, J.Amer.Chem.Soc., **69**, 326 (1947).

(7) W.S. Puvelich and R.W. Taft, Jr., J.Amer.Chem.Soc., **79**, 4935 (1957).

(8a) J. Vaiga, M. Luuk and A. Tuulmets, Organic Reactivity (Tartu) VIII, 27 (1971).

(8b) In ref. 8a the authors use E_S° in their correlations. This is a steric parameter related to E_S by the relationship $E_S^\circ = E_S - 0.20\ (3 - n_H)$, 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 by V.A. Pal'm in "Fundamentals of the Quantitative Theory of Organic Chemistry", Lenningrad 1967, Chapter X (in Russian).

(9) J.E. Dubois, C. Lion and M. Boussu, Tetrahedron Letters, 829 (1971).

(10) J.E. Dubois and M. Boussu, Unpublished results.