

[CONTRIBUTION FROM THE BAKER LABORATORY OF CHEMISTRY AT CORNELL UNIVERSITY]

The Relative Reactivity of Various Functional Groups toward a Grignard Reagent

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The fact that Grignard reagents react readily with a wide variety of functional groups frequently constitutes a serious objection to the use of polyfunctional compounds in synthetic work. Nevertheless, in a number of instances the selective reaction of organomagnesium halides upon bifunctional compounds, such as aldehyde esters¹ and keto esters,² has met with some success. Since little definite information is available concerning the relative reactivity of various functional groups it seemed of interest to compare a number of the more common ones.

The relative reactivity of a series of ketones toward methylmagnesium iodide has been determined by Hibbert,³ using α -naphthol as the reference substance. In this work a mixture of each ketone and α -naphthol was treated with methylmagnesium iodide and the volume of methane evolved was measured. The reactivity factor of the ketone was taken to be inversely proportional to the quantity of methane produced. Gilman and his collaborators⁴ have reported studies of the relative reactivity of several Grignard reagents with a miscellany of reactants. Their method consisted in determining the time required for complete reaction of a Grignard reagent with the reactant. Since a number of the latter undergo an almost instantaneous reaction, this method was of limited application for comparison of the reactants.

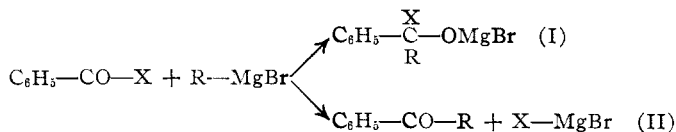
The method employed in the present work consisted in effecting a competitive reaction of phenylmagnesium bromide upon a mixture of two reactants. A solution of one equivalent of the Grignard reagent was added slowly to a solution containing one equivalent of each reactant. The reaction mixture was hydrolyzed and from an examination of the resulting products the unreacted portion of each reactant was found. Nine reactants, each having a phenyl radical attached to the functional group, were chosen for comparison and various pairs of these were examined (Table I).

Due to experimental difficulties and errors inherent in the method the results can be considered merely as an approximate order of reactivity for the several functional groups. It was found that accurate results could not be obtained except by direct comparison of two reactants: indirect comparisons using a reference substance were used only in those cases in which the reactants could not be compared directly. The relative

(1) Noller and Adams, *THIS JOURNAL*, **48**, 1074 (1926).(2) Grignard, *Ann. chim.*, [7] **27**, 548 (1902).(3) Hibbert, *J. Chem. Soc.*, **101**, 341 (1912).(4) Gilman, St. John and Heck, *Rec. trav. chim.*, **49**, 212 (1930).

reactivities observed were: $-\text{CHO} > -\text{COCH}_3 > -\text{NCO} > -\text{COF} > -\text{COC}_6\text{H}_5, -\text{COCl}, -\text{COBr} > -\text{CO}_2\text{C}_2\text{H}_5 > -\text{C}\equiv\text{N}$.

The order of activity of the three acid halides, benzoyl fluoride, chloride and bromide, is of particular interest because of its bearing upon the mechanism of the action of Grignard reagents upon acid derivatives. Either one of two reactions may occur in the initial stage of the reaction: addition to the carbonyl group (I) or direct replacement of the halogen atom (II).



If the reaction follows the second mechanism, one would expect the acid fluoride to be the least reactive of the three halides. Since the acid fluoride is actually found to be the most reactive, it is obvious that the reaction occurs through addition to the carbonyl group and not through a meta-thetical reaction of the halogen atom.⁵ By analogy it seems likely that esters and acid anhydrides likewise undergo addition to the carbonyl group as the first stage of the reaction.

In a previous investigation dealing with the preparation of ketones from acid derivatives and the Grignard reagent⁶ it was found that acid chlorides (and anhydrides) could be used satisfactorily for this purpose but that esters could not. A comparison of the relative reactivities gives clearly the explanation for this difference. Due to the fact that the ester is less reactive than the ketone produced by the initial reaction, the ketone is converted to the tertiary alcohol before another molecule of ester undergoes reaction. With an acid halide, which is of about the same reactivity as the ketone, subsequent reaction of the Grignard reagent does not occur exclusively with the ketone.

Information concerning the relative reactivities of the functional groups reported here is of preparative value in the choice of compounds to be used in effecting preferential reactions with bifunctional reactants. The selective action of Grignard reagents upon several bifunctional reactants has been used successfully for the synthesis of branched chain keto acids of high molecular weight.⁷

Experimental

General Procedure.—The reactions were effected in a 1-liter three-necked flask fitted with a mechanical stirrer, separatory funnel and condenser. The apparatus was rinsed with dry ether before using and the usual precautions were observed to exclude

(5) This conclusion confirms a suggestion made from a consideration of steric hindrance in the reaction of a substituted benzoyl chloride with methylmagnesium chloride [Fuson, Bertetti and Ross, *THIS JOURNAL*, **54**, 4381 (1932)].

(6) Nilanidhi, Dawson and Johnson, unpublished data.

(7) Work of C. R. Fordyce and R. C. Tallman in this Laboratory.

atmospheric moisture. The requisite quantities (0.12–0.16 mole) of the two reactants to be compared were dissolved in 150 cc. of dry ether in the reaction flask; in the separatory funnel was placed 25 cc. of ether and 100 cc. of a standard solution of phenylmagnesium bromide was added from a pipet. The Grignard reagent was allowed to drop slowly into the reaction flask at 20°, during the course of two and one-half hours. The separatory funnel was rinsed with 25 cc. of ether, and the stirring was continued for one-half hour longer. The mixture was decomposed by iced hydrochloric acid and the resulting mixture was agitated thoroughly. The ether layer was separated and washed twice with small portions of cold dilute hydrochloric acid and with water. The subsequent procedure for isolating the unchanged reactants or products of the reaction was varied according to the nature of the particular substances present. In general the results in the table are calculated from the recovery of the initial reactants rather than from the products of the reaction.

TABLE I
COMPETITIVE REACTIONS WITH PHENYLMAGNESIUM BROMIDE

A ^a	Competitive reactants B	Moles C ₆ H ₅ MgBr used	Molar ratio A/B	Percentage recovery	
				A	B
C ₆ H ₅ —COCH ₃	C ₆ H ₅ —CHO	0.146	1	66	27
	C ₆ H ₅ —COC ₆ H ₅	.146	1	10 ^b	90
	C ₆ H ₅ —COF ^f	.129	1	36 ^b	59 ^c
	C ₆ H ₅ —COCl	.146	1	33 ^b	63 ^c
C ₆ H ₅ —COC ₆ H ₅	C ₆ H ₅ —COF	.125	1	64 ^d	32 ^c
	C ₆ H ₅ —COF	.125	2	48 ^d	4 ^c
	C ₆ H ₅ —COCl	.129	1	47 ^d	52 ^c
	C ₆ H ₅ —COCl	.125	2	50 ^d	13 ^c
	C ₆ H ₅ —COBr	.160	1	48 ^d	51 ^c
	C ₆ H ₅ —COBr	.129	2	35 ^d	8 ^c
	C ₆ H ₅ —CO ₂ C ₂ H ₅	.146	1	8 ^d	94 ^c
	C ₆ H ₅ —CN	.146	1	0 ^d	98
C ₆ H ₅ —CN	C ₆ H ₅ —CO ₂ C ₂ H ₅	.131	1	92	63
	C ₆ H ₅ —CO ₂ C ₂ H ₅	.146	2	98	0
C ₆ H ₅ —NCO	C ₆ H ₅ —CHO	.146	1	92 ^e	5
	C ₆ H ₅ —COCH ₃	.146	1	75 ^e	19
	C ₆ H ₅ —COC ₆ H ₅	.146	1	6 ^e	78

^a The quantity of reactant A used was always equivalent to the phenylmagnesium bromide; the quantity of reactant B is indicated in the fourth column.

^b Acetophenone was separated by simple steam distillation and weighed as the oxime; benzophenone was separated by distillation with superheated steam.

^c Calculated from the benzoic acid produced by hydrolysis of the unchanged reactant.

^d Calculated from the benzophenone actually recovered minus that produced from the portion of reactant B which had reacted.

^e Calculated by difference, from the benzanilide produced.

^f Benzoyl fluoride was prepared in 50% yield by heating benzoyl chloride and potassium biferrous in a copper flask. The product was always washed with sodium bicarbonate solution, dried, and distilled (in glass apparatus) immediately before use; b. p. 151° (uncorr.) at 736 mm.

Summary

By means of competitive reactions with phenylmagnesium bromide, the relative reactivity of nine functional groups has been determined.

The bearing of these results upon the mechanism of certain Grignard reactions and the use of bifunctional reactants is discussed.

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Orientation in the Furan Nucleus. VI. β -Substituted Furans

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Introduction

The only established case of the directing influence of a mono- β -substituted furan is the aldehyde reaction effected by Reichstein and co-workers¹ on 3-methylfuran. They showed that the aldehydic group, introduced by hydrogen cyanide and hydrogen chloride, entered the 2-position to give 3-methyl-2-furfural. Oxidation of this compound gave the known 3-methyl-2-furoic acid.

The results now reported on the nitration and halogenation of β -mono-substituted furans make it possible to formulate with some confidence generalizations on the directing influence of such substituents. These may be stated as follows. (1) The entering group goes largely, if not exclusively, to one of the α -positions. (2) The particular α -position assumed by the substituent is determined largely by the nature of the group already in the β -position. If the group in the β -position is one which in benzene is largely *o,p*-directing, then the substituent assumes that α -position contiguous to the β -group; and if the group in the β -position is one which in benzene is largely *m*-directing, then the substituent assumes the more distant or opposite α -position.² With additional studies involving nuclear substitution under varied conditions, it would not be surprising to find some cases where the substituent goes to each α -position. Furthermore, in view of some anomalous substitution reactions with diphenylene oxide, there is the possibility that a sulfonic acid group, for example, might not assume the same position as a nitro group or a halogen. However, the rules as stated for β -substituted furans are sufficiently well established to warrant the prediction that mono-substitution of a compound like 4-methyl-3-furoic acid will involve the replacement of hydrogen on the 5-

(1) Reichstein, Zschokke and Goerg, *Helv. Chim. Acta*, **14**, 1277 (1931).

(2) It is significant that the rules for orientation of β -substituted furans may apply generally to di- α -substituted furans having unlike groups. For example, the sulfonation of 5-chloro-2-furoic acid gives 5-chloro-4(?) -sulfo-2-furoic acid and this compound with phosphorus pentachloride gives a dichlorofuroic acid identical with the compound previously described as 3,5-dichloro-2-furoic acid. The explanation (Ref. 3) involving 1,4-elimination of halogen hydride to account for the formation of 4,5-dihalogen-2-furoic acids rather than 3,5-dihalogen-2-furoic acids can be supplemented by two 1,2-eliminations, the second of which occurs subsequent to rearrangement of the α -hydrogen to the 3-position.