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REACTION OF MIXED CARBOXYLIC ANHYDRIDES WITH GRIGNARD REAGENTS. A CONVENIENT METHOD FOR THE PREPARATION OF 1,4- OR 1,6-DIKETONES

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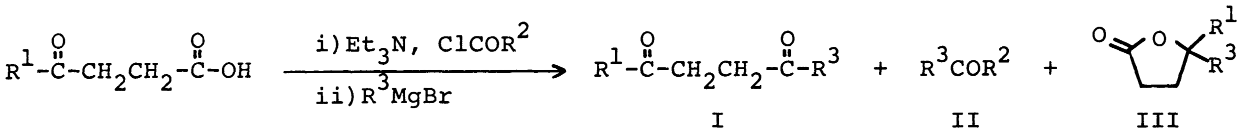
It was found that mixed carboxylic anhydrides of γ- or ε-oxocarboxylic acids react with Grignard reagents to give 1,4- or 1,6-diketones in 32∼71% yields by one step procedure.

The reaction of carboxylic anhydrides with Grignard reagents is not suited to the synthesis of ketones because tertiary alcohols, undesirable by-products, are always produced along with the ketones. Newmann et al.[1] reported that ketones were obtained in good yields when simple carboxylic anhydrides were allowed to react with Grignard reagents at below -70°C. The preferential formation of ketones was explained by the stabilities and the diminished solubilities of the addition product formed from Grignard reagents and carboxylic anhydrides at low temperature. Kammann et al.[2] found that formic acetic anhydride reacts with Grignard reagents to give aldehydes in 7∼39% yields along with ketones and alcohols.

In the previous paper,[3] a convenient method for the preparation of ketones from Grignard reagents and 2-pyridyl thioates was reported, and it was pointed out that the co-ordination complex of the two reagents played an important role in the preferential formation of ketones.

In the present experiment, it was established that the reaction of mixed carboxylic anhydrides, easily prepared from oxocarboxylic acids and acid chlorides, with Grignard reagents provides a convenient method for the synthesis of diketones. By this method, 1,4- or 1,6-diketones are produced from free γ- or ε-oxocarboxylic acids by one step procedure without protection of carbonyl group of the oxocarboxylic acids. For example, to a solution of levulinic acid (10 mmol) in 90 ml of dry THF was added triethylamine (10 mmol) and pivaloyl chloride (10 mmol) in this order at -30°C. After stirring for 20 minutes at -20∼-30°C, a THF solution containing 10 mmol of n-hexylmagnesium bromide was added at -78°C. The resulted reaction mixture was stirred for 30 minutes at -78°C and hydrolyzed with 10% aqueous ammonium chloride. After usual work-up, 2,5-dioxoundecane and 2,2-dimethyl-3-oxononane were isolated by silica gel column chromatography in 71 and 11% yields, respectively. In a similar manner, various diketones were isolated using ethyl (or isobutyl) chlorocarbonate as an acid chloride in 32∼64% yields as shown in Table 1. In addition, it was found that 1,6-diketone such as 1-phenyl-1,6-dioxoheptane was successfully obtained in 69% yield from 6-oxoheptanoic acid and phenylmagnesium bromide.

Table 1. Reaction of Mixed Carboxylic Anhydrides with Grignard Reagents



R^1	R^2	R^3	Solv.	Temp(°C)	Isolated Yield I(%)	II(%)	III(%)
CH_3	C_2H_5O	$n\text{-}C_6H_{13}$	ether	-5	32	17	2
CH_3	$i\text{-}C_4H_9O$	$n\text{-}C_6H_{13}$	ether	-20	39	28	2
CH_3	C_2H_5O	$n\text{-}C_6H_{13}$	THF	-78	40[a]	44	
CH_3	C_2H_5O	Ph	THF	-78	64		
CH_3	$i\text{-}C_4H_9O$	$n\text{-}C_6H_{13}$	THF	-78	32[a]	58	
Ph	C_2H_5O	Ph	THF	-78	63		
Ph	$i\text{-}C_4H_9O$	Ph	THF	-78	59		
CH_3	$(CH_3)_3C$	$n\text{-}C_6H_{13}$	THF	-78	71	11	

a) I and II were isolated as a mixture and their ratio was determined by NMR.

Different from the reaction[4] of organocadmium compounds with mixed carboxylic anhydrides, the present reaction affords diketones in fairly good yields by successive addition of Grignard reagents to mixed carboxylic anhydrides without removal of triethylamine hydrochloride.

Mixed carboxylic anhydrides used in this experiment have three reaction sites (a, b, and c in Fig. 1.) toward Grignard reagents leading to the formation of three products as esters or ketones (II), diketones (I), and lactones (III). Grignard reagents may form a chelate complex between two carbonyl groups (a and b) more easily as compared with the formation of a co-ordination complex with the carbonyl group c. The chelate complex affords a diketone or an ester by the internal nucleophilic attack of carbanion (R^3) to the carbonyl carbon a or b through the favorable six-membered intermediate, followed by the smooth elimination of magnesium ethyl (or isobutyl) carbonate (or magnesium carboxylate) as sketched in Fig. 1. Thus, diketones or esters result as major products by the preferential attack of Grignard reagents to the carbonyl group b or a.

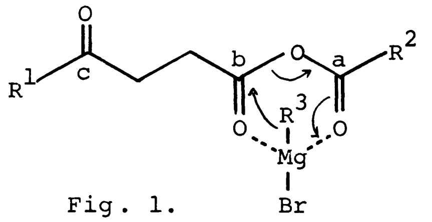


Fig. 1.

Further, the result obtained by using pivaloyl chloride suggests that the choice of a suitable substituent (R^2) would lead to a possible selection of the reaction site (a or b) in the above mechanism to vary the products ratio of diketones and esters. Further study is now under investigation and will be reported soon.

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