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REACTION OF MIXED CARBOXYLIC ANHYDRIDES WITH GRIGNARD REAGENTS. A USEFUL METHOD FOR THE PREPARATION OF KETONES

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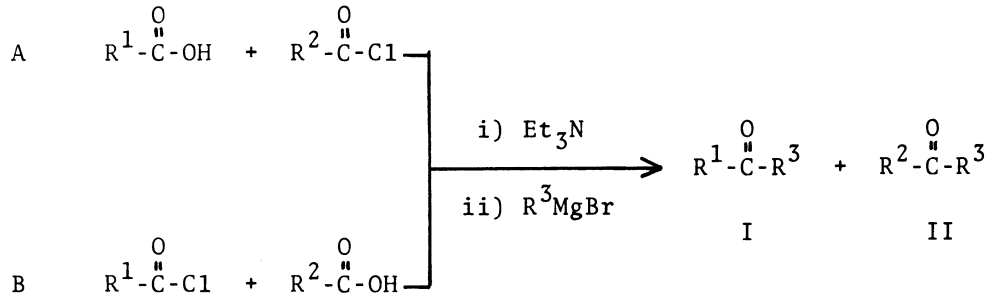
It was found that common ketones were prepared in good yields by the reaction of grignard reagents with mixed carboxylic anhydrides composed of o-substituted benzoic acids or pivalic acid and common carboxylic acids at -20 or -78°C. Further, it was established that a 1,4-diketone such as 2,5-dioxoundecane, a precursor of dihydrojasmone was synthesized in 71 ∿ 82% yields from levulinic acid by one step procedure without protecting its carbonyl group.

It is generally known that the reaction of carboxylic anhydrides with Grignard reagents is not suited to the synthesis of ketones owing to the formation of tertiary alcohols as by-products. However, Newmann and Smith[1] reported that ketones were obtained in good yields when simple carboxylic anhydrides such as acetic anhydride and benzoic anhydride 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. On the other hand, few reports have appeared on the reaction of mixed carboxylic anhydrides with Grignard reagents except in the case of the reaction of acetic formic anhydride forming aldehydes in 7 ∿ 39% yields along with ketones and alcohols reported by Edwards and Kammann.[2]

In the preceding paper,[3,4] the preparation of ketones from 2-pyridyl thioates and Grignard reagents 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. Based on this consideration, it was further found that 1,4- or 1,6-diketones are produced in fairly good yields along with esters by the treatment of

Grignard reagents with mixed carboxylic anhydrides from γ- or ε-oxocarboxylic acids and chloroformic esters. The esters were formed by the attack of Grignard reagents on the carbonic carbonyl group in mixed carboxylic anhydrides. The products ratio of the diketones and the esters was expected to increase by employing hindered carboxylic acid chlorides in place of chloroformic esters. Expectedly, the yield of 2,5-dioxoundecane was increased to 71% by the reaction of levulinic pivalic anhydride with n-hexylmagnesium bromide.

In this communication, a useful method for the preparation of common ketones and a 1,4-diketone by utilizing mixed carboxylic anhydrides composed of carboxylic acids and o-substituted benzoic acids or pivalic acid is described. The mixed carboxylic anhydrides were prepared by either of two methods (A or B), where R^2 is tertiary butyl or o-substituted phenyl group such as 2,6-dichlorophenyl, 2,4-dichlorophenyl, o-methoxyphenyl or o-ethoxyphenyl.



In a typical experiment by the procedure B, to a THF solution (90 ml) of o-anisic acid (10 mmol) were added triethylamine (10 mmol) and 3-phenylpropionyl chloride (10 mmol) in this order at -30°C. The resulted mixture was kept at -20 ∿ -30°C with stirring for 20 minutes and cooled at -78°C. To the reaction mixture was added an ether solution of phenylmagnesium bromide (10 mmol) during 10 minutes. After stirring for 10 minutes at -78°C, the reaction mixture was hydrolyzed with 10% aqueous ammonium chloride. 3-Phenylpropiophenone was isolated in 92% yield by silica gel chromatography after usual work-up. In a similar manner, various ketones were prepared in good yields from carboxylic acids (method A) or carboxylic acid chlorides (method B) by one step procedure as shown in Table 1.

Table 1. Reaction of Mixed Carboxylic Anhydrides with Grignard reagents at -78°C in THF.

Method	R^1	R^2	R^3	Isolated Yield (%) I	II
A	$C_6H_5CH_2CH_2$	t-C_4H_9	C_6H_5	73	
A	$C_6H_5CH_2CH_2$	2,4-$Cl_2C_6H_3$	C_6H_5	69	23
A	$CH_3COCH_2CH_2$	t-C_4H_9	n-C_6H_{13}	71	11
A	$CH_3COCH_2CH_2$	2,4-$Cl_2C_6H_3$	n-C_6H_{13}	74	24
A	$CH_3COCH_2CH_2$	o-$CH_3OC_6H_4$ [a]	n-C_6H_{13}	82	<11
A	$CH_3COCH_2CH_2$	o-$C_2H_5OC_6H_4$ [b]	n-C_6H_{13}	77	11
B	$C_6H_5CH_2CH_2$	2,6-$Cl_2C_6H_3$	C_6H_5	93	
B	$C_6H_5CH_2CH_2$	o-$CH_3OC_6H_4$	C_6H_5	92	
B	$C_6H_5CH_2CH_2$	o-$CH_3OC_6H_4$	C_6H_5	95	
B	$C_6H_5CH_2CH_2$	2,6-$Cl_2C_6H_3$	$C_6H_5CH_2CH_2$	86	
B	$C_6H_5CH_2CH_2$	o-$CH_3OC_6H_4$	$C_6H_5CH_2CH_2$	83	
B	C_6H_5	o-$CH_3OC_6H_4$	$C_6H_5CH_2CH_2$	79	
B	$C_6H_5CH_2CH_2$	o-$CH_3OC_6H_4$	C_6H_5	72 [c]	

a) In the case of o-anisoyl chloride, the formation of mixed carboxylic anhydride is so slow as compared with the other acid chlorides that the reaction mixture was stirred for 2 hours before the addition of Grignard reagent.

b) From the same reason as a) the mixed carboxylic anhydride was prepared by adding levulinic acid to the mixture of o-ethoxybenzoyl chloride and triethylamine at 0 ∿ -5°C. The resulted mixture was stirred for 2 hours at 0 ∿ -5°C.

c) Reaction with Grignard reagent was carried out at -20°C.

As listed in Table 1, common ketones and 1,4-diketone were obtained in good yields from carboxylic acids and carboxylic acid chlorides by one step procedure without removal of the triethylamine hydrochloride formed. Further, in the case of the preparation of a 1,4-diketone such as 2,5-dioxoundecane, levulinic acid was used without protection of the carbonyl group. This diketone was converted to

dihydrojasmone in 89% yield by the method of Hunsdieker.[5] Namely, dihydrojasmone was prepared in high yield by two steps procedure from levulinic acid.

The above results may be explained by assuming an initial formation of the chelate complexes from mixed carboxylic anhydrides and Grignard reagents. The complexes are in turn converted into ketones by the internal nucleophilic attack of carbanion (R^3) on the carbonyl carbon through a favorable six-membered intermediate, followed by the smooth elimination of magnesium carboxylates as sketched in Fig. 1. The alternative route to afford R^2COR^3, however, was strongly suppressed by the steric hindrance of o-substituted phenyl or tertiary butyl group.

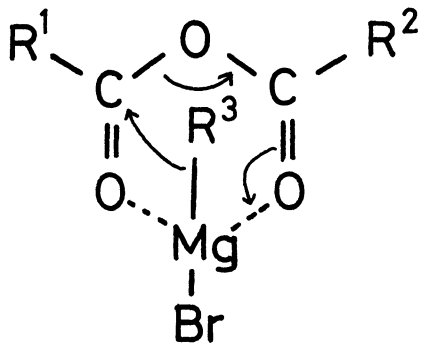


Fig. 1.

Further study on the application of this method is now under investigation.

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