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SIMPLE AND CHEMOSELECTIVE SYNTHESIS OF KETONES FROM CARBOXYLIC ACIDS AND GRIGNARD REAGENTS USING DICHLOROTRIPHENYLPHOSPHORANE

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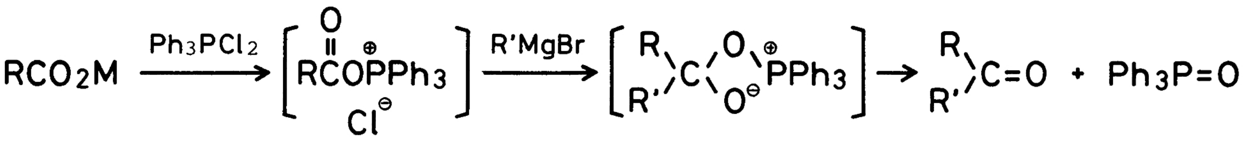
Dichlorotriphenylphosphorane was found to be a good condensation reagent for synthesis of ketones from carboxylic acids and Grignard reagents under mild conditions. Synthetic utility of the present method is demonstrated by the chemoselective reaction of carboxylic acids possessing such a functional group as halogen, cyano, or carbonyl.

It has been known that dihalotriphenylphosphorane reacts with carboxylic acids to give the corresponding acyl halides in high yields.$^{1)}$ This communication outlines an extension of this method to a simple and high-yield method for ketone synthesis from carboxylic acid by the formation of a new carbon-carbon bond. In general, the condensation reaction of organometallics with acylating reagents is used most frequently in a laboratory for ketone synthesis.$^{2)}$ The most troublesome side reaction in the condensation is a simultaneous formation of tertiary alcohols, which is formed by the further reaction of the organometallics with the ketones yielded, and various methods have been devised by design of acylating reagents to prevent such a side reaction. For example, mixed carboxylic anhydrides of pivalic acid or *o*-substituted benzoic acid$^{3)}$ and carboxylic diphenylphosphonic anhydride$^{4)}$ are employed in such condensations. We now wish to describe here a simple synthesis of ketones from carboxylic acids and Grignard reagents using dichlorotriphenylphosphorane under mild conditions.

Dihalotriphenylphosphorane, prepared easily from triphenylphosphine and halogen, reacts with a carboxylic acid to form acyloxyphosphonium salt **1** as an intermediate, of which carbonyl group is susceptible of an attack of nucleophiles by the inductive effect of the phosphonium group. Accordingly by the use of Grignard reagents, the easily available and popular organometallics, as the nucleophiles, a simple and chemoselective ketone synthesis is expected *via* betain **2** like the intermediate of the Wittig reaction. Since the reaction of free carboxylic acids with dihalotriphenylphosphorane liberates a hydrogen halide by the formation of a carboxyphosphonium salt, metal carboxylates were used to avoid the liberation of the strong acidic substance. Thus, to a suspension of lithium benzoate in THF was added a solution of dihalotriphenylphosphorane in dichloromethane at -30 °C, and then a solution of β-phenethylmagnesium bromide was added at the same temperature. After a usual workup, dichlorotriphenylphosphorane gave 95% yield of β-phenethyl phenyl ketone, although dibromotriphenylphosphorane gave the same ketone in only 32% yield.$^{5)}$ Lithium salt gave better result than sodium salt (89% yield) and potassium salt (88% yield), because of the solubility of the salts. From the results of examination for molar ratio of the reactants, the optimal amount of the Grignard reagent was 1.5 equivalents to the carboxylate. It is noteworthy than no formation of tertiary alcohol was observed, in spite of the excess use of the Grignard reagent. Accordingly, the present reaction is considered to proceed by a nucleophilic attack of Grignard reagent on the carbonyl group of carboxyphosphonium salt 1 intermediately formed giving a stable betain 2, and not to proceed *via* acyl chloride formed by the reaction of carboxylic acid with dichlorotriphenylphosphorane. In fact, the reaction of benzoyl chloride with β-phenethyl Grignard reagent at -30 °C gave the ketone in 52% yield along with 1,3,5-triphenyl-3-pentanol in 12% yield.



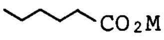
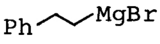
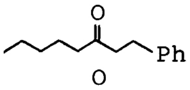
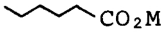
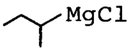
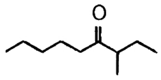
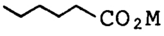
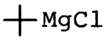
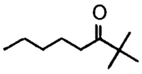
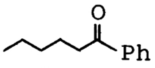
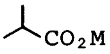
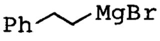
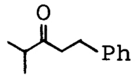
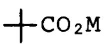
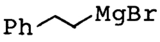
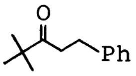
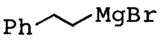
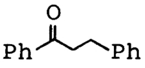
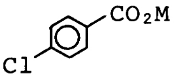
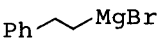
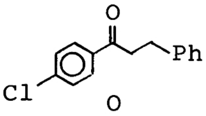
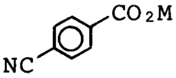
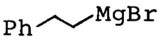
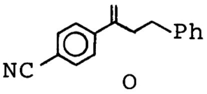
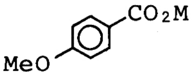
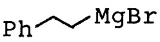
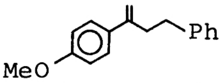
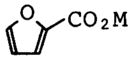
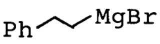
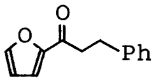
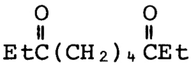
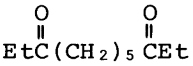
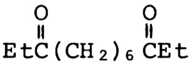
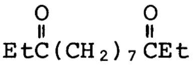
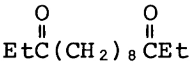
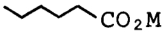
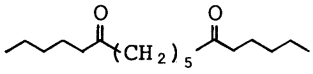
1 2

Instead of lithium carboxylates, free carboxylic acids can be used by combination with an amine as a base. Triethylamine was more suitable in the present reaction than other amines such as tributylamine and pyridine. In this case, 2.5 equivalents of the Grignard reagents were required, because the reagent reacts with an ammonium chloride generated *in situ*.

The result of the reaction of various kinds of carboxylic acids or their lithium salts with the Grignard reagents was summarized in Table 1. In all cases, no formation of tertiary alcohols could be observed. The yields of the ketones using lithium carboxylate were superior to that using free carboxylic acids and triethylamine. Although bulkiness of the substituent in the carboxylic acids or the Grignard reagents influenced the yield of the ketones, even pivalic acid or *t*-butyl Grignard reagent with tertiary substituent gave the corresponding ketones in good yields of 63 — 65%. Similarly, aromatic carboxylic acids without or with a substituent of halogen, methoxy, or cyano group and heteroaromatic carboxylic acids such as furoic acid were converted to the corresponding ketones in high yields by the present method. In addition, the present method is effective for the synthesis of diketones. The reaction of dilithium dicarboxylate and 2.3 equivalent of ethylmagnesium bromide gave high yields of symmetric diketones. Similary di-Grignard reagent such as 1,5-pentyldimagnesium dibromide also reacted with hexanoyltriphenylphosphonium chloride formed *in situ* by the reaction of lithium hexanoate and dichlorotriphenylphosphorane to give 6,12-octadecanedione in a yield of 91%.

The reaction using carboxyphosphonium salt provides a means for chemoselective ketone synthesis as shown in Table 2. When half methyl ester of adipinic acid was treated with β-phenethylmagnesium bromide using dichlorotriphenylphosphorane in the presence of triethylamine, methyl 6-oxo-8-phenyloctanoate was obtained in a yield of 65%. In the same manner, the carboxylic acids with cyano or bromine group were also converted chemoselectively to the corresponding ketones in good yields. Furthermore, lithium 6-oxooctanoate, a carboxylate with carbonyl group, gave 1-

Table 1. Yields of Ketones by the Reaction of Carboxylic Acids with Grignard Reagents Using Dichlorotriphenylphosphorane[a]

Run	Acid	Grignard Reagent	Ketone[b]	Yield(%)	
				M = Li[c]	M = H[d]
1				95	66
2				83	71
3				65	57
4		PhMgBr		58	
5				84	48
6				64	63
7	$PhCO_2M$			95	90
8				94	
9					72
10				91	
11				92	
12	$MO_2C(CH_2)_4CO_2M$	EtMgBr	 $\mathrm{Et\overset{O}{\overset{\|}{C}}(CH_2)_4\overset{O}{\overset{\|}{C}}Et}$	80	
13	$MO_2C(CH_2)_5CO_2M$	EtMgBr	 $\mathrm{Et\overset{O}{\overset{\|}{C}}(CH_2)_5\overset{O}{\overset{\|}{C}}Et}$	91	
14	$MO_2C(CH_2)_6CO_2M$	EtMgBr	 $\mathrm{Et\overset{O}{\overset{\|}{C}}(CH_2)_6\overset{O}{\overset{\|}{C}}Et}$	83	
15	$MO_2C(CH_2)_7CO_2M$	EtMgBr	 $\mathrm{Et\overset{O}{\overset{\|}{C}}(CH_2)_7\overset{O}{\overset{\|}{C}}Et}$	82	
16	$MO_2C(CH_2)_8CO_2M$	EtMgBr	 $\mathrm{Et\overset{O}{\overset{\|}{C}}(CH_2)_8\overset{O}{\overset{\|}{C}}Et}$	92	
17		$BrMg(CH_2)_5MgBr$		91	

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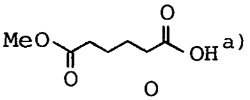
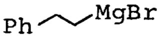
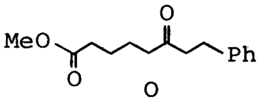
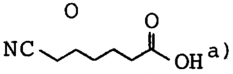
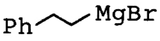
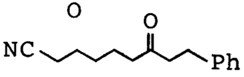
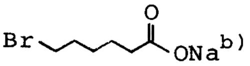
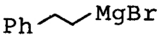
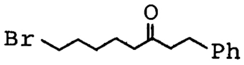
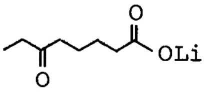
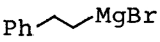
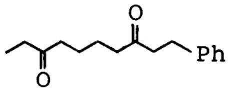
[a] All reactions were performed on 1 mmol scale with the same procedure as described in the text. Lithium salts were prepared from the corresponding carboxylic acids and lithium hydroxide. [b] All products were isolated by silica-gel TLC and identified by IR and NMR spectra. [c] The molar ratio of dichlorotriphenylphosphorane, lithium carboxylate and Grignard reagents was 1.2:1:1.5. [d] When free carboxylic acids were used, the molar ratio of dichlorotriphenylphosphorane, carboxylic acids, triethylamine and Grignard reagents was 1.2:1:1.2:2.5.

phenyl-3,8-decanedione in 72% yield.

Table 2. Chemoselectivity in the Ketone Synthesis Using Dichlorotriphenylphosphorane

Run	Acid	Grignard Reagent	Product	Yield(%)
18	 a)			65
19	 a)			60
20	 b)			82
21				72

a) Using 1.2 eq Et_3N and 2.3 eq Grignard reagent. b) Prepared from acid and NaH.

A representative procedure for the synthesis of 1-phenyl-3-octanone is as follows. To a solution of dichlorotriphenylphosphorane (3.1 ml of 0.387 M CH_2Cl_2 solution 1.2 mmol) was added a suspension of lithium hexanoate in THF (7 ml) at -30 °C under an argon atmosphere, and the reaction mixture was stirred for 1 h at the same temperature. Then to the mixture was added a solution of β-phenethylmagnesium bromide (1.9 ml of 0.779 M THF solution 1.5 mmol). After stirring for 1 h the reaction was quenched by the addition of 2 M HCl aq solution. The organic layer was extracted with ether, washed with $NaHCO_3$ aq solution, and dried over $MgSO_4$. After removal of the solvent, the residue was chromatographed on silica-gel TLC (hexane:ether = 7:1, Rf = 0.6) to give 1-phenyl-3-octanone in 95% yield.

In conclusion, dichlorotriphenylphosphorane, prepared easily from triphenylphosphine and chlorine, is an effective condensation reagent for the synthesis of ketones from carboxylic acids and the Grignard reagents in good yields with high chemoselectivity under mild conditions and in one-pot operation.

References

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3) M. Araki and T. Mukaiyama, *Chem. Lett.*, 1974, 663.
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