

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

Tamotsu FUJISAWA,\* Sachio IIDA, Hiroshi UEHARA, and Toshio SATO  
Chemistry Department of Resources, Mie University, Tsu, Mie 514


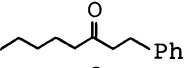

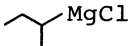
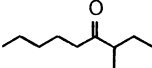

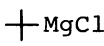
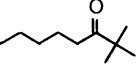
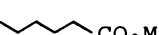
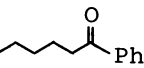
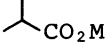
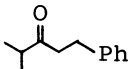
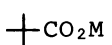
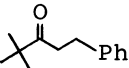
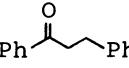
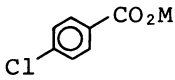
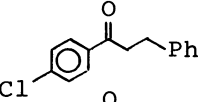
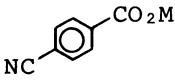
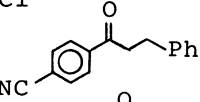
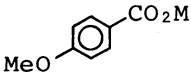
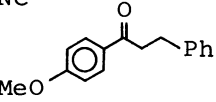
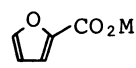
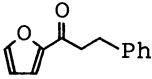
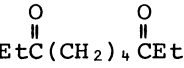
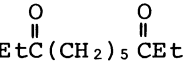
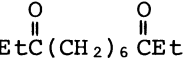
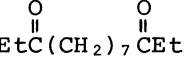
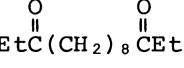
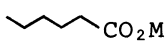
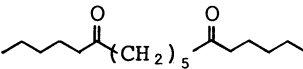
Dichlorotriphenylphosphorane was found to be a good condensation reagent for synthesis of ketones from carboxylic acids and Grignard reagents under mild conditions. Synthetic utility of the present method is demonstrated by the chemoselective reaction of carboxylic acids possessing such a functional 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.<sup>1)</sup> 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.<sup>2)</sup> 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<sup>3)</sup> and carboxylic diphenylphosphonic anhydride<sup>4)</sup> 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  $\beta$ -phenethylmagnesium bromide was added at the same temperature. After a usual workup, dichlorotriphenylphosphorane gave 95% yield of  $\beta$ -phenethyl phenyl ketone, although dibromotriphenylphosphorane gave the same ketone in only 32% yield.<sup>5)</sup> Lithium salt gave better result than sodium salt (89% yield)



Table 1. Yields of Ketones by the Reaction of Carboxylic Acids with Grignard Reagents Using Dichlorotriphenylphosphorane<sup>a)</sup>

Run	Acid	Grignard Reagent	Ketone <sup>b)</sup>	Yield(%)	
				M = Li <sup>c)</sup>	M = H <sup>d)</sup>
1		Ph-CH <sub>2</sub> -CH <sub>2</sub> -MgBr		95	66
2				83	71
3				65	57
4		PhMgBr		58	
5		Ph-CH <sub>2</sub> -CH <sub>2</sub> -MgBr		84	48
6		Ph-CH <sub>2</sub> -CH <sub>2</sub> -MgBr		64	63
7	PhCO <sub>2</sub> M	Ph-CH <sub>2</sub> -CH <sub>2</sub> -MgBr		95	90
8		Ph-CH <sub>2</sub> -CH <sub>2</sub> -MgBr		94	
9		Ph-CH <sub>2</sub> -CH <sub>2</sub> -MgBr			72
10		Ph-CH <sub>2</sub> -CH <sub>2</sub> -MgBr		91	
11		Ph-CH <sub>2</sub> -CH <sub>2</sub> -MgBr		92	
12	MO <sub>2</sub> C(CH <sub>2</sub> ) <sub>4</sub> CO <sub>2</sub> M	EtMgBr		80	
13	MO <sub>2</sub> C(CH <sub>2</sub> ) <sub>5</sub> CO <sub>2</sub> M	EtMgBr		91	
14	MO <sub>2</sub> C(CH <sub>2</sub> ) <sub>6</sub> CO <sub>2</sub> M	EtMgBr		83	
15	MO <sub>2</sub> C(CH <sub>2</sub> ) <sub>7</sub> CO <sub>2</sub> M	EtMgBr		82	
16	MO <sub>2</sub> C(CH <sub>2</sub> ) <sub>8</sub> CO <sub>2</sub> M	EtMgBr		92	
17		BrMg(CH <sub>2</sub> ) <sub>5</sub> MgBr		91	

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		Ph-CH <sub>2</sub> -MgBr		65
19		Ph-CH <sub>2</sub> -MgBr		60
20		Ph-CH <sub>2</sub> -MgBr		82
21		Ph-CH <sub>2</sub> -MgBr		72

a) Using 1.2 eq Et<sub>3</sub>N 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<sub>2</sub>Cl<sub>2</sub> 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<sub>3</sub> aq solution, and dried over MgSO<sub>4</sub>. After removal of the solvent, the residue was chromatographed on silica-gel TLC (hexane:ether = 7:1, R<sub>f</sub> = 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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