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ONE-POT SYNTHESIS OF KETONES FROM CARBOXYLIC ACIDS AND GRIGNARD REAGENTS USING N,N-DIPHENYL-p-METHOXYPHENYLCHLOROMETHYLENIMINIUM CHLORIDE

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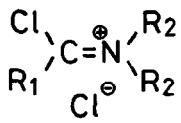
Summary: *N,N-Diphenyl-p-methoxyphenylchloromethyleniminium chloride is found to be an effective condensation reagent of carboxylic acids and Grignard reagents under mild conditions to afford the corresponding ketones in high yields.*

In general, a condensation reaction most frequently used to prepare ketones in the laboratory is the reaction of organometallics with acylating reagents. As the latter reagents, acid halides,[1] esters,[2] acid anhydrides,[3] nitriles,[4] *N*-acylimidazoles,[5] 2-pylidilthioesters,[6] and 8-acyloxyquinolines[7] are employed and in some cases carboxylic acids themselves are used. Other starting materials are various kinds of organometallics constructing from lithium, magnesium, copper, cadmium, and so on. 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 ketones yielded, and various methods have been devised to prevent such a side reaction using designed acylating reagents In the use of carboxylic acids, the most prototype in acylating reagents, only one combination with organolithium compounds is well known.[8] However the method results in also the formation of tertiary alcohols, although the reaction with methyl- or aryllithium compound to yield ketones in high yields. If Grignard reagents, the most available and popular reagent in organometallics, react with carboxylic acids to give ketones, this reaction has a wide applicability in organic synthesis. We now wish to describe here one-pot synthesis of ketones from carboxylic acids and Grignard reagents using *N,N*-diphenyl-*p*-methoxyphenylchloromethyleniminium chloride.

The reason aimed at the iminium salt as the condensation reagent is that carboxyiminium salt 2 prepared easily from chloroiminium salt 1 and carboxylic acids may be very reactive by the inductive effect of the iminium group. Further easy formation of chloroiminium salt 1 with various substituents from the corresponding carboxamides is also one of the reasons. For the ketone synthesis



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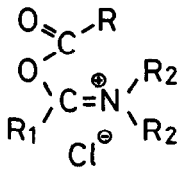

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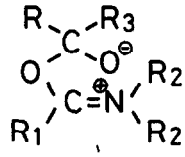

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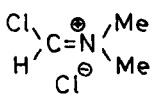
by the reaction of the carboxymethyleniminium salt 2 with the Grignard reagents, a formation of a stable intermediate of betain 3 is expected to avoid the formation of tertiary alcohol. This stability of the betain 3 may be controlled by an effect of the substituents of the iminium salts. Thus the reaction of carboxylic acids and the Grignard reagents using various kinds of chloromethylenеiminium chloride 1 was examined. The following salts were prepared from the corresponding amides or urea and oxalyl chloride, and were subjected to the reaction with lithium caproate in THF-CH_2Cl_2 at -30 °C. Then, 5 mol% of copper(I) iodide and a solution of β-phenethylmagnesium bromide was added into the carboxymethyleniminium chloride at 0 °C to give 1-phenyl-3-octanone. The use of *N*,*N*-dimethylchloromethyleniminium chloride (4) and *N*,*N*,*N'*,*N'*-tetramethylchloroformamidinium chloride (5) gave the desired ketone in 64% and 2% yields, respectively, while aromatic iminium salts gave good results. *N*,*N*-Diphenylphenylchloromethyleniminium chloride (6) and *N*,*N*-diphenyl-*p*-chlorophenylchloromethyleniminium chloride (7) afforded the ketone in yields of 74% and 89%, respectively. The best result was obtained by the use of *N*,*N*-diphenyl-*p*-methoxyphenylchloromethyleniminium chloride (8) as the condensation reagent to give the ketone in 94% yield. In the absence of the copper(I) catalyst, the yield of 1-phenyl-3-octanone decreased to 74% even using the methoxyphenyliminium salt 8. When the reaction was carried out at -78 °C using the methoxyphenyliminium salt 8, the desired ketone was obtained only 33% yield accompanying with *N*,*N*-diphenylamine and β-phenethyl *p*-methoxyphenyl ketone in the yields of 17% and 13%, respectively, which were produced by the attack of the Grignard reagent at the iminium carbon. However, when the reaction was carried out at 0 °C, the desired ketone was obtained in a high yield by the exclusive attack of the organometallic compound to the carboxyl carbon.

The result of the reaction of various kinds of carboxylic acids and the Grignard reagents was summarized in Table. When free carboxylic acids were used, two equivalents of the Grignard reagents were required, because free hydrogen



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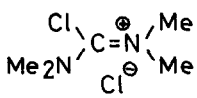

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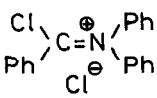

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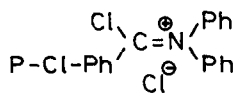

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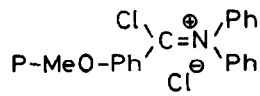

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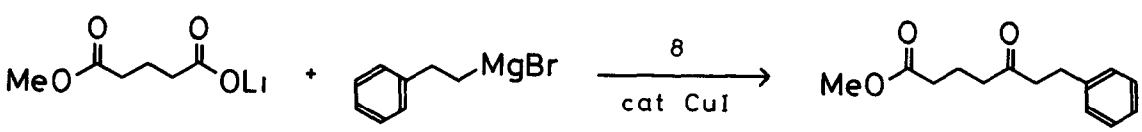
Table. Yields of Ketones by the Reaction of Carboxylic Acids with Grignard Reagents Using *N*,*N*-Diphenyl-*p*-Methoxyphenylchloromethyleniminium Chloride[a]

Acid	Grignard Reagent	Ketone[c]	Yield (%)	Acid	Grignard Reagent	Ketone[c]	Yield (%)
~~COOH	Ph~~MgBr[b]	~~C(=O)~~Ph	81	~~COOLi	PhMgBr	~~C(=O)~~Ph	66
~~COONa	Ph~~MgBr	~~C(=O)~~Ph	85	⟙COOLi	Ph~~MgBr	⟙C(=O)~~Ph	88
~~COOLi	Ph~~MgBr	~~C(=O)~~Ph	94	⬡-COOLi	Ph~~MgBr	⬡-C(=O)~~Ph	86
~~COOLi	⟙MgCl	~~C(=O)⟙	71	+COOLi	Ph~~MgBr	+C(=O)~~Ph	77
~~COOLi	+MgCl	~~C(=O)+	60	PhCOOLi	Ph~~MgBr	Ph-C(=O)-Ph	86

[a] All reactions were performed on 2 mmol scales with the same procedure as described in the text. Lithium salts were prepared from the corresponding carboxylic acids and lithium hydroxide. [b] The molar ratio of the acid and the Grignard reagent is 1:2. [c] All products were isolated by silica gel TLC and identified by IR and NMR spectra.

chloride was liberated in the coupling stage of 8 and carboxylic acids, and two equivalents of the metal chloride were formed. In the use of metal carboxylate such as sodium or lithium carboxylate, one equivalent of the Grignard reagents was enough to obtain the desired ketones. Although bulkiness of the substituents in the carboxylic acids influenced the yield of the ketones, even pivalic acid with tertiary substituent gave the corresponding ketone in a high yield of 77%. On the other hand, the bulkiness of the substituents in the Grignard reagents showed a considerable effect on the yield, and *t*-butylmagnesium chloride gave the corresponding ketone in a yield of 60%.

It is noteworthy that only carboxylic acid moiety was successfully activated to be converted into ketone moiety by the present method. When half methyl ester of glutaric acid lithium salt was condensed with β-phenethylmagnesium bromide using *N*,*N*-diphenyl-*p*-methoxyphenylchloromethyleniminium chloride in the presence of a copper(I) catalyst, methyl 5-oxo-7-phenylheptanoate was obtained in a yield of 69%.



In addition, an acid-sensitive functional group could not be influenced. Levulinic acid with a ketal function gave 2,2-ethylenedioxy-5-undecanone, which

is the precursor of dihydrojasmone, by the reaction with hexylmagnesium chloride using the condensation reagent in a yield of 70%.

The representative procedure for the synthesis of 1-phenyl-3-octanone is as follows. To a solution of *N*,*N*-diphenyl-*p*-methoxybenzamide (2 mmol) in dichloroethane (3 ml) was added oxalyl chloride (1 ml) and the solution was heated at 60 °C for overnight. After the solvent and excess oxalyl chloride was removed under a reduced pressure, a suspension of lithium hexanoate (2 mmol) in dichloromethane (3 ml) and THF (8 ml) was added to the residue at -30 °C, and the reaction mixture was stirred for 1 h at the same temperature. Then the mixture was warmed to 0 °C, and a suspension of 5 mol% of copper(I) iodide in THF and a solution of β-phenethylmagnesium bromide (2.52 ml of 0.79M THF solution, 2 mmol) was subsequently added to the reaction mixture. After stirring for 1 h, the reaction was quenched by the addition of 2M 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, hexane was added into the residue and *N*,*N*-diphenyl-*p*-methoxybenzamide was filtered off. The filtrate was evaporated and 1-phenyl-3-octanone was obtained by silica gel TLC (hexane:ether = 10:1) in 94% yield.

In conclusion, *N*,*N*-diphenyl-*p*-methoxyphenylchloromethyleniminium chloride, prepared easily from *N*,*N*-diphenyl-*p*-methoxybenzamide and oxalyl chloride, is an effective condensation reagent for the synthesis of ketones from carboxylic acids and the Grignard reagents in high yields under mild conditions and in one-pot operation.

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