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HIGHLY CHEMOSELECTIVE SYNTHESIS OF KETONES FROM CARBOXYLIC ACIDS AND GRIGNARD REAGENTS USING α-CHLOROENAMINES AS A CONDENSATION REAGENT

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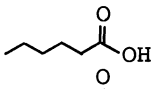
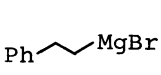
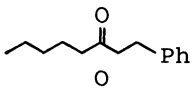
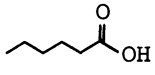
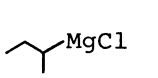
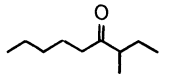
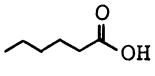
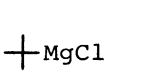
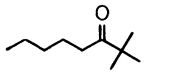
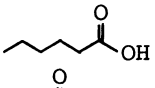
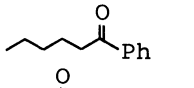
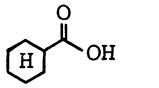
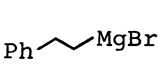
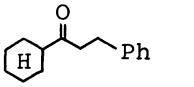
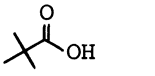
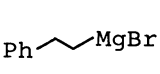
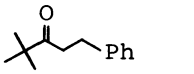
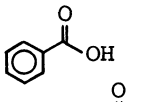
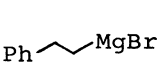
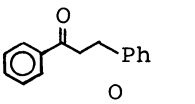
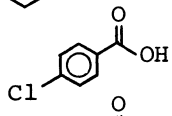
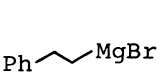
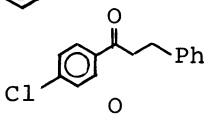
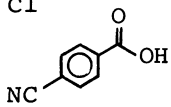
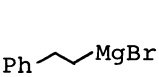
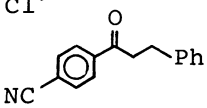
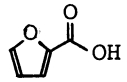
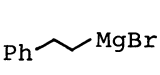
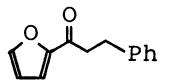
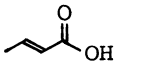
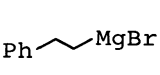
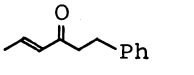
α-Chloroenamines are found to be an effective condensation reagent of carboxylic acids and Grignard reagents under mild conditions to afford chemoselectively the corresponding ketones in high yields and in one-pot operation.

Condensation reactions of organometallics with acylating reagents have provided an important method for ketone synthesis. Most of them, however, consist of two steps involving troublesome transformation of carboxylic acids to activated acylating reagents.[1] One-pot ketone synthesis from carboxylic acids and Grignard reagents[2] has been achieved by activation of carboxylic acids *in situ via* mixed acid anhydrides,[3] carboxyphosphonium salt,[4] or carboxymethyleniminium salt using *N*,*N*-diphenyl-*p*-methoxyphenylchloromethyleniminium chloride[5] reported by us. In the latter method, the use of lithium carboxylates was generally recommended because the reaction of free carboxylic acids with the chloromethyleniminium chloride liberates hydrogen chloride which consumes one equivalent of Grignard reagents. If equimolar amounts of free carboxylic acids and Grignard reagents give chemoselectively ketones in high yields, the method would have a wide applicability in organic syntheses. We now wish to report here one-pot and chemoselective synthesis of ketones by an equimolar reaction of free carboxylic acids with Grignard reagents using an α-chloroenamines as a condensation reagent. α-Chloroenamines,[6] prepared easily by the treatment of chloroiminium salts with triethylamine, are known to react with carboxylic acids to form reactive carboxymethyleniminium chloride *in situ* without liberation of hydrogen chloride. Accordingly, one equivalent of Grignard reagents is enough to obtain ketones in one-pot operation, when α-chloroenamines are used as an activating reagent of carboxylic acids.

Carboxylic acid was treated with 1-chloro-*N*,*N*,2-trimethylpropenylamine[6c] (α-chloroenamine A) at 0 °C for 3 h in a mixture of THF and dichloromethane, and 5 mol% of copper(I) iodide and Grignard reagent were then added at the same temperature and stirred for 1 h. The yields of various kinds of ketones synthesized from carboxylic acids and Grignard reagents by this method were summarized in Table 1. When α-chloroenamine A was used in the reaction of carboxylic acids and Grignard reagents with bulky substituents, the use of 1.2 molar equivalents of α-chloroenamine A and Grignard reagent gave better results than the use of one molar equivalent of them. Although pivalic acid with a tertiary substituent gave the corresponding ketone in a low yield, the reaction using 1-chloro-2-methyl-*N*,*N*-tetramethylenepropenylamine (α-chloroenamine B) at room

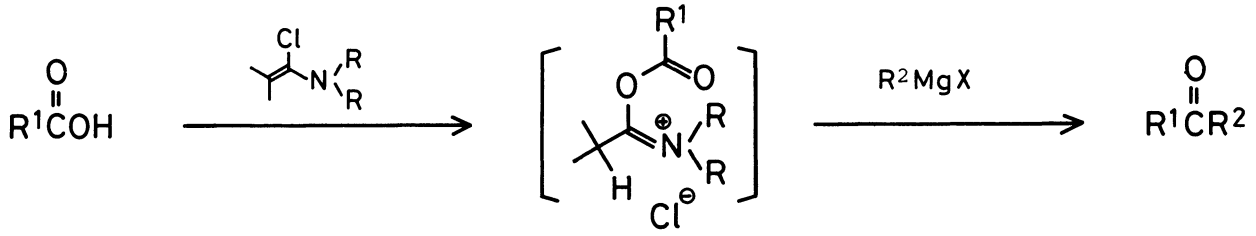
Table 1. Yields of Ketones by the Reaction of Carboxylic Acids with Grignard Reagents Using α-Chloroenamines[a)]

Acid	Grignard reagent	Product[b)]	Yield/% A	Yield/% B
			90	90
			74 (82)[c)]	77
			65 (68)[c)]	65
	PhMgBr		44 (46)[c)]	46
			79 (84)[c)]	81
			10	80[d)]
			85	85
			85	83
			79	74
			70 (85)[c)]	85
			23	20

a) All reactions were performed on 1 mmol scale with the same procedure as described in the text. b) Products were isolated by silica-gel TLC and identified by IR and NMR spectra. c) In these cases, 1.2 molar equivalents of Grignard reagents and the chloroenamine were used. d) This reaction was carried out at room temperature.

temperature increased the yield of the ketone. In the reaction of aromatic carboxylic acids, benzoic acids without or with substituent of chlorine or cyano group, or 2-furoic acid gave the corresponding ketones in high yields. Vinyl or allyl Grignard reagents, however, did not give the corresponding ketones, although the reaction of phenyl Grignard reagent with hexanoic acid gave the corresponding ketone in 46% yield. Crotonic acid gave the corresponding unsaturated ketone in a low yield. Without the copper catalyst, the yields of the ketones were decreased.

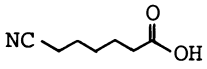
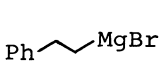
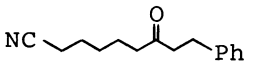
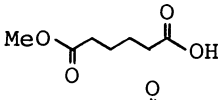
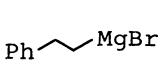
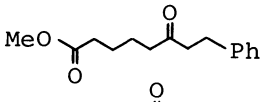
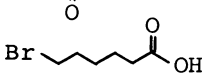
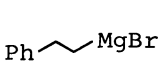
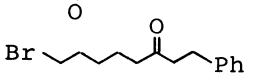
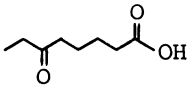
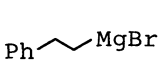
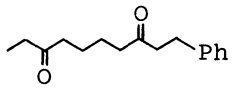
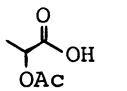
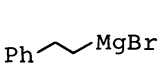
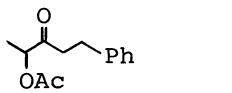
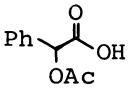
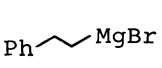
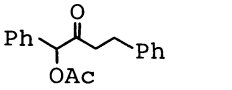
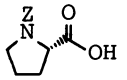
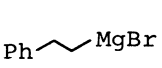
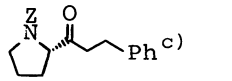
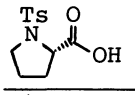
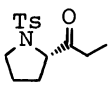
The mild reaction conditions of the present method using α-chloroenamines make a chemoselective synthesis of ketones possible. The results for the reaction of various functionalized carboxylic acids were summarized in Table 2. Even in the reaction of carboxylic acids with various functional groups such as cyano, ester and bromine, only carboxylic acid moiety could be converted chemoselectively to the corresponding ketones. Furthermore, a carbonyl group, which is known to react



easily with Grignard reagents, was tolerant by the present method, and a diketone was obtained in a high yield from a ketocarboxylic acid. α-Acetoxycarboxylic acids and *N*-protected prolines gave the corresponding ketones in high yields, and no racemization was observed in the reaction of *N*-tosyl-L-proline. This is reasonably explained in terms of positive charge on carboxymethyleniminium chloride which activates strongly the carbonyl group on it to accelerate an attack of Grignard reagent to the carbonyl group.

A representative procedure for the synthesis of 1-phenyl-3-octanone is as follows. To a solution of α-chloroenamine A (1 mmol) in dichloromethane (1.4 ml) was added a solution of hexanoic acid (1 mmol) in THF solution (3 ml) at 0 °C, and the reaction mixture was stirred for 3 h at the same temperature. Then, 5 mol% of copper(I) iodide and a solution of β-phenethylmagnesium bromide (1.39 ml of 0.72 M THF solution, 1 mmol) were added to the reaction mixture. After stirring for 1 h, the reaction was quenched by the addition of 2 M HCl aq solution. The organic

Table 2. Yields of Ketones from Grignard Reagents and Carboxylic Acids with Various Functional Groups[a)]

Acid	Grignard reagent	Product[b)]	Yield/%
			88
			82
			87
			80
			80
			83
		 [c)]	83
	EtMgBr	 [d)]	80

a) All reactions were performed using α-chloroenamine A on 1 mmol scale. b) The products were isolated by silica-gel TLC and identified by IR and NMR spectra. c) $[\alpha]_D^{23}$ -60.0° (c 0.08, $CHCl_3$). d) $[\alpha]_D^{23}$ -156° (c 0.0218, $CHCl_3$).[7)]

layer was extracted with ether, washed with $NaHCO_3$ aq solution, and dried over $MgSO_4$. After removal of the solvent, 1-phenyl-3-octanone was obtained by silica gel TLC (hexane:ether = 10:1) in 90% yield.

Thus, α-chloroenamine is found to be an effective condensation reagent for one-pot ketone synthesis from carboxylic acids and Grignard reagents. The following advantages make the present method more attractive and more widely applicable than the previous method using *N*,*N*-diphenyl-*p*-methoxyphenylchloromethyleniminium chloride:[5] 1) The condensation reagent, α-chloroenamine is easily prepared, stored, and handled in a dichloromethane solution, while the iminium chloride should be prepared just before use; 2) The use of equimolar Grignard reagents to carboxylic acids is sufficient for the reaction; and 3) Higher chemoselectivity is realized in the present method.

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