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REACTION OF (E)-PHENYL 2-PYRIDYL KETONE O-ACYLOXIMES (PPAO) WITH GRIGNARD REAGENTS. A CONVENIENT AND HIGHLY CHEMOSELECTIVE SYNTHESIS OF KETONES

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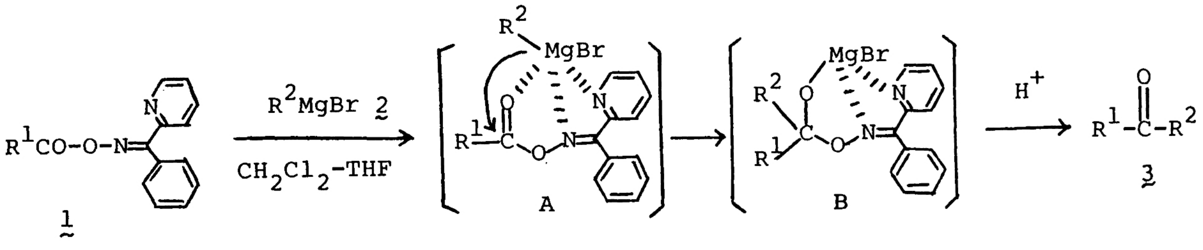
The reaction of (E)-phenyl 2-pyridyl ketone O-acyloximes (PPAO) with Grignard reagents was found to be widely applicable to the chemoselective synthesis of various ketones in good yields under mild conditions.

The condensation reaction of organometallics with acylating reagents is widely used fundamental method for ketone synthesis. Therefore, a number of synthetic methods for the preparation of ketones from Grignard reagents and carboxylic acid derivatives have been reported.$^{1,2)}$ However, tertiary alcohols are generally formed as undesirable by-product. Recently, various methods have been reported by design of acylating reagents to prevent such a side reaction.$^{3-5)}$ One of the most effective solutions of the problem was reported by Mukaiyama,$^{5)}$ a method for the synthesis of ketones from Grignard reagents and "S-(2-pyridyl) thioates" through an intermediate of "S-(2-pyridyl) thioate" magnesium complex.

In recent years, we have focused our interest on the utilization of metal chelating agents as functional leaving groups. We achieved a highly chemoselective synthesis of carboxamides using (E)-phenyl 2-pyridyl ketone O-acyloximes (PPAO).$^{6)}$ In the course of investigation, we found that PPAO can be easily activated by some metals such as Cu^{2+} and Fe^{3+}, and amides from sterically hindered carboxylic acid and amine were easily obtained. We now wish to report here an alternative convenient method for the highly chemoselective synthesis of ketones from PPAOs and Grignard reagents.

PPAOs can be easily prepared from carboxylic acid or carboxylic acid chloride, and (E)-phenyl 2-pyridyl ketone oxime (PPKO) in quantitative yield as mentioned before.[6)] The reactions of PPAOs with Grignared reagents smoothly proceeded to afford the corresponding ketones in high yields under mild conditions. the facility of the reaction may be explained by assuming the initial formation of a complex A,[5)] which is immediately converted to another complex B to afford the corresponding ketones by treating with acid as shown in Scheme 1.

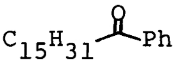
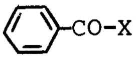
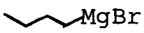
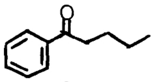
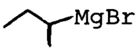
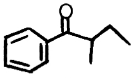
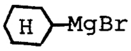
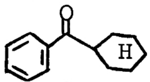
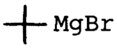
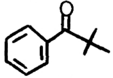
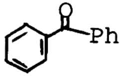
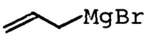
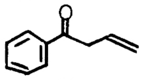
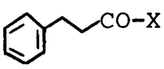
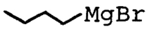
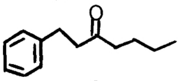
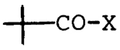
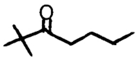
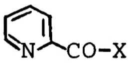
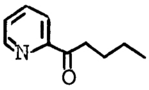
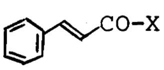
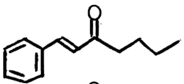
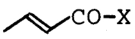
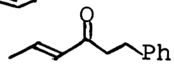
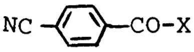
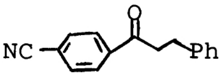
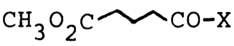
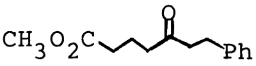
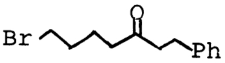
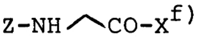
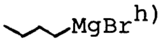
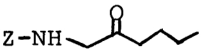
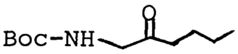


Scheme 1.

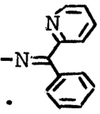
A typical procedure for Ketone synthesis is as follows: To a solution of PPAO **1a** (436 mg, 1 mmol) in dry CH_2Cl_2 (5 ml) was added a THF solution of phenylmagnesium bromide (approximately 1 mol equiv.) until PPAO **1a** disappeared (checked by TLC) at 0 °C under N_2 atmosphere. The reaction was quenched by the addition of 0.2 ml of water. The organic layer was extracted with ether, washed with 5% HCl aq. solution to remove PPKO, and dried over Na_2SO_4. After evaporation of the solvent, purification of the residue by silica gel flush column chromatography (Hexane : Et_2O = 9 : 1) gave ketone **3a** (269 mg, 85%). In a similar manner, various ketones were prepared as summarized in Table 1.

It was found that the present reaction is widely applicable to the preparation of ketones in good yields. Even from sterically hindered PPAO **1d** and Grignard reagent **2e** (entries 9 and 5 in Table 1), the corresponding ketones **3i** and **3e**, respectively, were easily obtained. Furthermore, the reaction of allyl Grignard reagent **2f** with PPAO **1b** gave the corresponding ketone **3g** in 76% yield under refluxed conditions. In the case of PPAOs **1f** and **1g**, the corresponding unsaturated ketones **3k** and **3l** were obtained, and 1,4-addition did not occur (entries 11 and 12 in Table 1). Furthermore, even in the reaction of PPAOs with various functional groups such as cyano, ester and bromine, only carboxylic acid moiety could be converted chemoselectively to the corresponding ketones **3m**-**o**. In the case of PPAOs **1k** and **1l**, the corresponding ketones **3p** and **3q** were obtained. Benzyloxycarbonyl and t-butoxycarbonyl groups were tolerant in the present method.

Table 1. Reaction of various PPAOs with Grignard reagents[a)]

Entry	PPAO[b)]		Grignard reagent		Product[c)]		Yield/%
1	$C_{15}H_{31}CO$-X	1a	PhMgBr	2a		3a	85
2		1b		2b		3b	68
3	〃			2c		3c	72
4	〃			2d		3d	90
5	〃			2e		3e	50[d)]
6	〃		PhMgBr	2a		3f	81
7	〃			2f		3g	76[e)]
8		1c		2b		3h	73
9		1d	〃			3i	98
10		1e	〃			3j	85
11		1f	〃			3k	94
12		1g		2g		3l	61
13		1h	〃			3m	87
14		1i	〃			3n	75
15		1j	〃			3o	91
16		1k		2b		3p	70
17		1l	〃 h)			3q	81

a) All reactions were performed on 1 mmol scale with the same procedure as described in the text. b) X= O-N=



c) All the products gave satisfactory NMR and IR spectra.
d) R.t., overnight. e) Refluxed for 3 h. Ketone isomer (α,β-unsaturated ketone) was not obtained. f) Z- : benzyloxycarbonyl-. g) Boc- : t-butoxycarbonyl-.
h) 2 mol equiv. of Grignard reagent was used.

In conclusion, the preferential, highly chemoselective formation of ketones may be speculated as follows: 1) Since PPAOs capture magnesium atom of Grignard reagents and are activated by magnesium ion, only carboxylic acid moiety can be smoothly converted to the corresponding ketones under mild conditions. 2) Since the complex B is very stabilized by the coordination of nitrogen atoms of oxime and pyridine to the magnesium atom,7) further reaction with the Grignard reagents giving tertiary alchols is prevented.5)

References

1) T. Fujisawa, T. Mori, K. Higuchi, and T. Sato, Chem. Lett., 1983, 1791 and references cited therein.

2) C. Cardellicchio, V. Fiandanese, G. marchdse, and L. Ronzini, Tetrahedron Lett., 26, 3595 (1985).

3) H. A. Staab and E. Jost, Justus Liebigs Ann. Chem., 655, 90 (1962).

4) T. Sakan and Y. Mori, Chem. Lett., 1972, 793.

5) T. Mukaiyama, M. Araki, and H. Takei, J. Am. Chem. Soc., 95, 4763 (1973).

6) T. Miyasaka and S. Noguchi, Chem. Lett., 1985, 701.

7) The reaction mechanism and reactivity of PPAO are now investigated by X-ray crystallographic analysis and calculations using MNDOC method. These results show that PPKO well functions as a metal chelator in the course of the reaction. See T. Miyasaka, H. Monobe, M. Masuhara, Y. Tsuruta, S. Noguchi, T. Taga, K. Kajiwara, T. Ohbatake, and K. Fuji, 12th Synposium on Progress in Organic Reaction and Syntheses, Nagoya, November 1985, Synposium Papers p. 73.

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