A Convenient Method for the Preparation of Ketones by the Reaction of Grignard Reagents with Carboxylic Acid Derivatives

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It was found that ketones were prepared in excellent yields by the reaction of Grignard reagents with *S*-(2-pyridyl) thioates and their analogues or with 2-pyridyl esters. The mechanism of this reaction was also discussed. This useful method for the preparation of ketones was successfully applied to the syntheses of *cis*-jasmone and dihydrojasmone.

Many works have been reported on the synthesis of ketones from carboxylic acid derivatives and organometallic compounds.[1] The reaction of Grignard reagents with acid chlorides, nitriles, acid amides, or acid anhydrides is frequently employed for this purpose; however, tertiary alcohols, undesirable by-products, are invariably accompanied with the formation of ketones except in the case of nitriles.

Staab and Jost[2] reported that the treatment of Grignard reagents with *N*-acylimidazoles affords ketones in fairly good yields. Recently, a convenient method for the synthesis of ketones from Grignard reagents and 8-acyloxyquinolines was reported by Sakan and Mori.[3] The reaction was suggested to proceed through an important intermediate of 8-acyloxyquinoline metal complex.

As part of our study on the carbon-carbon bond forming reaction by the use of 2-pyridyl sulfides,[4] it was found that various *S*-(2-pyridyl) thioates react very rapidly with Grignard reagents to give ketones in excellent yields by simple procedures. The preliminary report of this work was published elsewhere.[5]

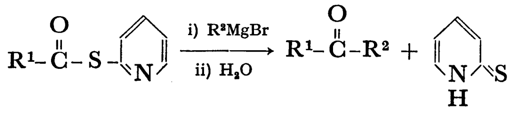
This paper describes a scope and a limitation of this useful method for the preparation of ketones by the reaction of Grignard reagents with *S*-(2-pyridyl) thioates and their analogues or with 2-pyridyl esters, and the application of this method to the syntheses of *cis*-jasmone and dihydrojasmone.

S-(2-Pyridyl) thioates of various carboxylic acids were prepared according to the following two methods; (A) the reaction of 2-pyridinethiol with carboxylic acid halides in the presence of tertiary amine such as triethylamine, or (B) the reaction of carboxylic acids with triphenylphosphine and 2,2′-dipyridyl disulfide.[6] In general, the reaction of *S*-(2-pyridyl) thioates with Grignard reagents was carried out in dry tetrahydrofuran (THF) at 0 °C under argon atmosphere by the inverse addition. Usual work-up afforded various ketones in excellent yields as shown in Table 1.

TABLE 1. REACTION OF *S*-(2-PYRIDYL) THIOATES WITH GRIGNARD REAGENTS IN THF

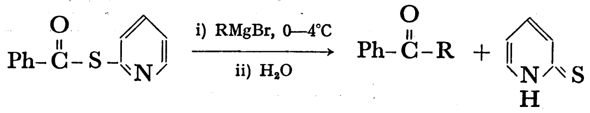
R^1	R^2	R^1-CO-R^2 (%)[a]	Mp °C, (Bp °C/mmHg)
Ph	Ph	quant.	46.0—47.0
CH_3	Ph	91	oil
n-C_5H_{11}	Ph	86	oil
n-C_5H_{11}	Ph	83[b]	(134—137/17)
$\{CH_2\}_4$	Ph[c]	92[d]	107.0—107.5
$PhCH_2CH_2$	n-C_4H_9	97	oil
$PhCH_2CH_2$	c-C_6H_{11}	95	oil
$PhCH_2CH_2$	sec-C_4H_9	83	oil
$C_2H_5OCO\{CH_2\}_4$	Ph	85	27.0—28.0
$CH_3CO\{CH_2\}_4$	Ph	73	42.0—43.0

a) Isolated yields by preparative tlc (silica gel). b) Isolated yield by distillation. c) Two molar amounts of phenylmagnesium bromide were used. d) The yield of 1,4-dibenzoylbutane.



The effects of the solvents on this reaction clearly indicate that THF is the most suitable solvent (see Table 2). In THF, the reaction proceeded in homogeneous solution throughout the addition of Grignard reagents. While, in the cases of other solvents, white precipitates immediately appeared when Grignard reagents were added to the solution of *S*-(2-pyridyl) thioates.

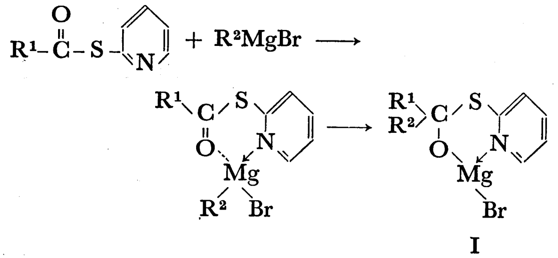
TABLE 2. SOLVENT EFFECT



R	Solvent	Ph-CO-R(%)[a]	R_2(Ph)COH(%)
Ph	THF	quant.	—
Ph	Ether	54[b]	18
Ph	Benzene	80[b]	4
n-C_4H_9	Benzene	74	

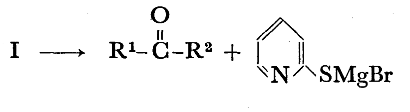
a) Isolated yields by preparative tlc (silica gel). b) The mixture of benzophenone and triphenylmethanol was isolated and their ratio was determined by glpc.

In the early stage of this study, it was assumed that the preferential formation of ketones would be accomplished by the formation of a stable six-membered intermediate **I** which would react very sluggishly with

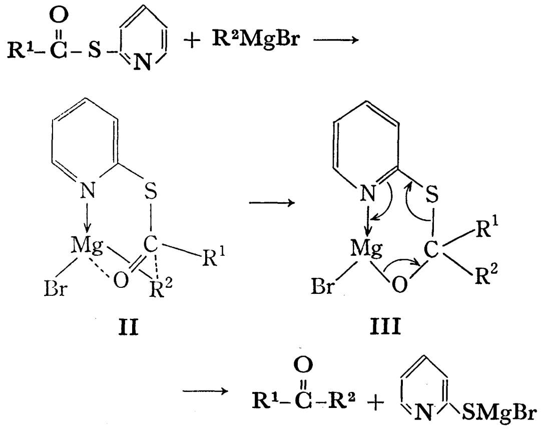


I

Grignard reagents as compared with *S*-(2-pyridyl) thioates. But, the IR spectra of the reaction mixture of *S*(2-pyridyl) isobutanethioate and cyclohexylmagnesium bromide in argon atmosphere showed the absorption at 1710 cm^{-1} which was assigned to the stretching vibration of the carbonyl group of the ketone. This result may indicates that the intermediate I is not kept stable under the reaction condition, but decomposes rapidly into ketones and magnesium thiolate. Thus, it can be concluded that the preferential formation of ketones by the present reaction depends only on the high reactivity of Grignard reagents toward *S*-(2-pyridyl) thioates as compared with ketones. This was confirmed by the following results; 1) benzophenone was obtained quantitatively by the reaction of *S*-(2-pyridyl) benzothioate with phenylmagnesium bromide in the presence of an equimolar amount of benzophenone without accompanying triphenylmethanol, and 2) the treatment of the *S*-(2-pyridyl) thioate of 6-oxoheptanoic acid or 5-carboethoxyvaleric acid with phenylmagnesium bromide without protection of the carbonyl group afforded the corresponding diketone or ketoester in high yields.



High reactivity of *S*-(2-pyridyl) thioates toward Grignard reagents would be attributed to the following three reasons; (1) Grignard reagents are activated by the formation of complex II with *S*-(2-pyridyl) thioates, (2) the addition reaction of Grignard reagents to the carbonyl group of *S*-(2-pyridyl) thioates proceeds through the favorable six-membered intermediate, (3) after the addition of Grignard reagents to the carbonyl group, magnesium thiolate IV is eliminated smoothly through electrocyclic mechanism as sketched in III.



II III

IV

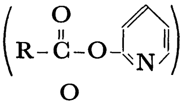
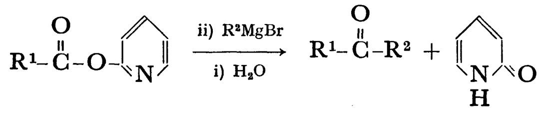
The above-mentioned mechanism indicates that 2-pyridyl esters  or the thioates having such a skelton as $R\text{–}\overset{O}{\overset{\|}{C}}\text{–}S\text{–}\overset{|}{C}\text{–}N\text{–}$ would similarly react with Grignard reagents to result in the exclusive formation of ketones. Expectedly, ketones were obtained in high yields by the addition of Grignard reagents to a THF solution of 2-pyridyl esters at 0 °C as shown in Table 3.

TABLE 3. REACTION OF 2-PYRIDYL ESTERS WITH GRIGNARD REAGENTS IN THF

R¹	R²	R¹COR²(%)	Mp(°C)
Ph	Ph	93	46.0—47.0
Ph	*n*-C_4H_9	77	oil
Ph	*c*-C_6H_{11}	97	53.0—55.0
$PhCH_2CH_2$	Ph	88	67.0—68.0
$PhCH_2CH_2$	*n*-C_4H_9	87	oil
$PhCH_2CH_2$	*c*-C_6H_{11}	88	oil
$PhCH_2CH_2$	*t*-C_4H_9	<64	oil

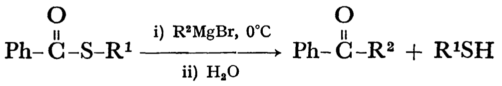
a) Isolated yields by preparative tlc (silica gel).



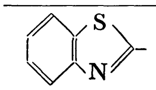
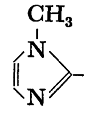
The IR spectra of the reaction mixture of 2-pyridyl benzoate and phenylmagnesium bromide in argon atmosphere showed the absorption at 1663 cm^{-1} assigned to the carbonyl group of benzophenone formed by the reaction.

The thioates obtained from benzoyl chloride and 2-benzothiazolethiol or 2-(*N*-methylimidazole)thiol also reacted with Grignard reagents to give ketones as shown in Table 4.

TABLE 4. REACTION OF THIOATES WITH GRIGNARD REAGENTS IN THF



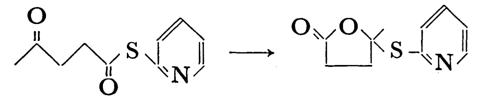
$$Ph\text{–}\overset{O}{\overset{\|}{C}}\text{–}S\text{–}R^1 \xrightarrow[\text{ii) }H_2O]{\text{i) }R^2MgBr,\ 0^\circ C} Ph\text{–}\overset{O}{\overset{\|}{C}}\text{–}R^2 + R^1SH$$

R¹	R²	Ph-CO-R²(%)	Mp (°C)
	Ph	98	46.0—47.0
	Ph	98	46.0—47.5
	n-C_4H_9	30[a)]	oil
	n-C_4H_9	70[b)]	oil

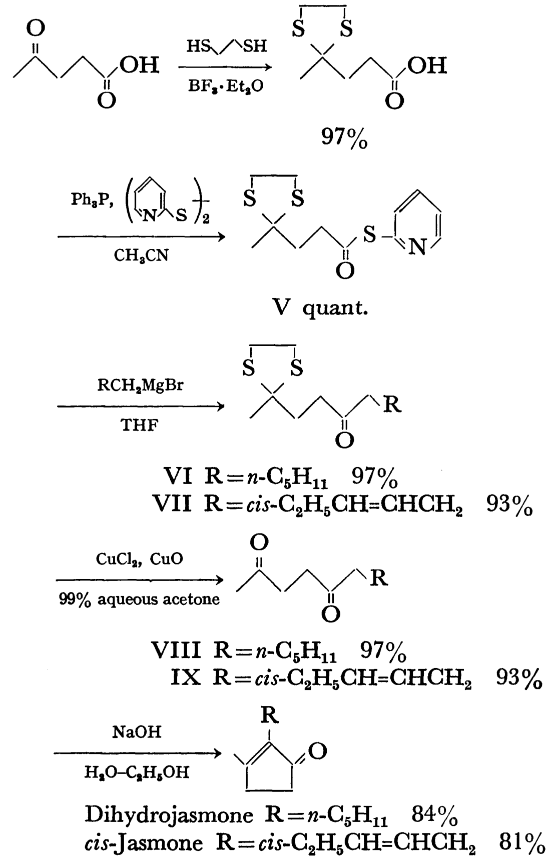
a) 1-Butyl-1-phenylpentanol was isolated in *ca.* 29% besides the ketone. b) Reaction at −78°C.

The present ketone synthesis by using *S*-(2-pyridyl) thioates was successfully applied to the preparation of *cis*-jasmone and dihydrojasmone through 1,4-diketones starting from levulinic acid as in Scheme 1.

In the above scheme, the protection of the carbonyl group by ethanedithiol seems to be unnecessary from the results shown in Table 1. But, *S*-(2-pyridyl) 6-oxopentanethioate (X), prepared by the reaction of levulinic acid with triphenylphosphine and 2,2′-dipyridyl disulfide, is not stable at room temperature and is readily converted to *γ*-pyridylthio-*γ*-valerolactone (XI).



X XI



Scheme 1. Syntheses of *cis*-jasmone and dihydrojasmone

Therefore, the carbonyl group was led to ethylene dithioacetal in order to isolate the pure thioate V. The thioate V was isolated by silica gel column chromatography in 97% yield based on levulinic acid. The ketone VI was obtained in 97% yield by the reaction of V with *n*-hexylmagnesium bromide, and the hydrolysis of VI by our method[7] afforded 1,4-diketone (VIII) in 98% yield. Dihydrojasmone was obtained from VIII according to the method of Hunsdieker[8] in 84% yield. Analogously, olefinic 1,4-diketone IX was isolated in 82% yield by the reaction of V with 3-*cis*-hexenyl magnesium bromide, followed by the deprotection of the carbonyl group.[7] IX was converted to *cis*-jasmone in 81% yield by the ordinary procedure.[8]

In conclusion, it is noted that all the common ketones were easily prepared in high yields without accompanying tertiary alcohols by treating *S*-(2-pyridyl) thioates and 2-pyridyl esters with Grignard reagents. Further, this procedure was proved to be applicable to the syntheses of 1,6-diketone as 1-phenyl-1,6-dioxoheptane without the protection of carbonyl group or 1,4-diketones as 2,5-dioxo-*cis*-8-undecene and 1,5-dioxoundecane, precursors of *cis*-jasmone and dihydrojasmone.

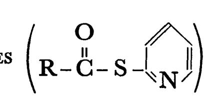
Experimental

All the melting points and boiling points are uncorrected.

General Method for the Preparation of S-*(2-Pyridyl) Thioates.* *S*-(2-Pyridyl) thioates were prepared by the following two methods. (A) To a solution of 2-pyridinethiol[9] (2.22 g, 20 mmol) and triethylamine (2.02 g, 20 mmol) in dry THF (30 ml) was added 20 mmol of an acid halide at 0 °C with stirring. The reaction mixture was stirred for 4 hr at room temperature. After removal of triethylamine hydrochloride by filtration, the solvent was removed under reduced pressure and the residue was dissolved in ether. The ether layer was washed with saturated sodium chloride solution and dried over sodium sulfate. Removal of the solvent gave a crude *S*-(2-pyridyl) thioate quantitatively. The crude thioate was purified by distillation or recrystallization. (B) To a mixture of 2,2′-dipyridyl disulfide (2.20 g, 10 mmol), triphenylphosphine (2.62 g, 10 mmol), and a carboxylic acid (10 mmol) was added dry acetonitrile (30 ml) at once with stirring. The reaction mixture was stirred for 10 min and then the solvent was removed under reduced pressure. The residue was chromatographed over silica gel to give a *S*-(2-pyridyl) thioate.

S-(2-Pyridyl) thioates obtained by the method A or B were listed in Table 5.

TABLE 5. *S*-(2-PYRIDYL)THIOATES



R	Method	Yield (%)	Mp °C (Bp °C/mmHg)
Ph	A	80	50.0—51.0[a)]
CH_3	A	60	(98—99/4)
n-C_5H_{11}	A	84	(111—112/1)
$PhCH_2CH_2$	A	82	56.0—58.0[b)]
$\{CH_2\}_4$	A	57	44.5—45.0[c)]
$CH_3CO\{CH_2\}_4$	A	80[d)]	oil
$C_2H_5OCO\{CH_2\}_4$	B	78[d)]	oil

Recrystallized from a) benzene–hexane, b) cyclohexane, c) ether. d) Purified by silica gel column chromatography.

Other Thioates. *S*-[2-(*N*-Methylimidazolyl)] benzothioate and *S*-(2-benzothiazolyl) benzothioate were prepared similarly according to the method A mentioned above using 2-(*N*-methylimidazole)thiol of 2-benzothiazolethiol instead of 2-pyridinethiol (74% mp 104.5—105.0 °C (benzene–hexane), 75% mp 125.0—126.0 °C (cyclohexane)).

2-Pyridyl Esters. To a mixture of 2-hydroxypyridine (0.951 g, 10 mmol) and triethylamine (1.012 g, 10 mmol) in 50 ml of dry ether was added benzoyl chloride (1.406 g, 10 mmol) at 0 °C with stirring. After stirring for 4 hr at room temperature, precipitated triethylamine hydrochloride was removed by filtration. The filtrate was washed with saturated sodium chloride solution and dried over sodium sulfate. Removal of the ether gave a solid, which was recrystallized from cyclohexane–hexane to afford 2-pyridyl benzoate (1.05 g, 53% mp 41.0—42.0 °C).

In a similar manner, 2-pyridyl *β*-phenylpropionate was prepared using *β*-phenylpropionyl chloride instead of benzoyl chloride in benzene as a solvent. It is necessary that the benzene solution containing 2-pyridyl *β*-phenylpropionate is dried quickly over sodium sulfate, since this ester is readily hydrolyzed. (68% bp 128—130 °C/1.3 × 10^{-1} mmHg).

General Procedure for the Reaction of Thioates with Grignard Reagents under Argon. In a 50 ml two-necked flask equipped with dropping funnel and gas inlet tube were placed 20 ml of dry THF and 2 mmol of a thioate. The flask was cooled in ice-water bath and a THF solution of Grignard reagent (approximately 1 equivalent) was added from the dropping funnel until the thioates were consumed (checked by tlc). The reaction mixture was quenched with 10% ammonium chloride and the resulting solution was extracted with ether. The organic layer was washed with 1 M sodium hydroxide to remove the thiol formed, with saturated sodium chloride and dried over sodium sulfate. After removal of the solvent the residue, almost pure ketone, was further purified by silica gel chromatography or distillation.

General Procedure for the Reaction of 2-Pyridyl Esters with Grignard Reagents under Argon. In 10 ml of THF a 2-pyridyl ester (1 mmol) was allowed to react with a Grignard reagent according to the above procedure. After quenching with 10% ammonium chloride, the resulting mixture was extracted with ether. The organic layer was washed with saturated sodium chloride and dried over sodium sulfate. After removal of the solvent the residue, whose IR spectra showed no absorption assigned to the stretching vibration of alcoholic O–H bond, was chromatographed over silica gel to give pure ketone.

Levulinic Acid Ethylene Dithioacetal. To a mixture of levulinic acid (0.231 g) and ethanedithiol (0.234 g) was added boron trifluoride etherate (0.2 ml) with stirring. An exothermic reaction occurred and after 2.5 hr, the resulting white solid was dissolved in ether. The ether layer was washed with water and dried over sodium sulfate. After removal of the ether, the obtained acid was purified by silica gel thin layer chromatography (0.370 g 97% mp 53.0—55.0 °C). In the case of larger scale experiment, recrystallization may be recommended instead of the chromatography.

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