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A CONVENIENT METHOD FOR THE DIRECT PREPARATION OF KETONES FROM 2-(6-(2-METHOXYETHYL)PYRIDYL) CARBOXYLATES AND ALKYL IODIDES BY USE OF ZINC DUST AND A CATALYTIC AMOUNT OF NICKEL DICHLORIDE

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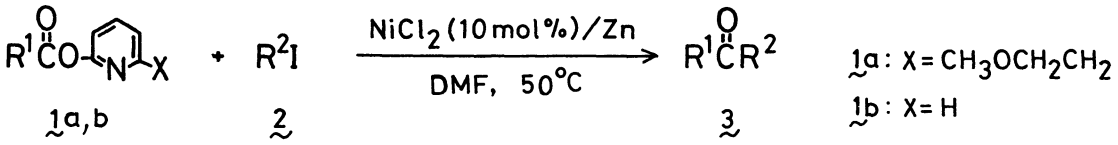
Treatment of 2-(6-(2-methoxyethyl)pyridyl) carboxylates with alkyl iodides in the presence of zinc dust and a catalytic amount of $NiCl_2$ in DMF at 50 °C affords unsymmetrical ketones in good yields by a one-pot procedure.

Reaction of organometallics with carboxylic acids or their derivatives is one of the most useful methods for the preparation of unsymmetrical ketones. For example, reactions of organolithium compounds[1] with carboxylic acids and reactions of organocopper[2] or organocadmium[3] reagents with acyl halides are widely employed. Treatment of Grignard reagents[4] with some active esters of carboxylic acids is also a useful method for the preparation of ketones. Previously we have reported that 2-pyridyl carboxylates or S-(2-pyridyl) thioates selectively produce ketones in good yields on treatment with Grignard reagents[5] or π-allylnickel complexes.[6] However, in these reactions it is necessary to prepare the organometallics independently prior to the use. Consequently we have been investigating a more convenient procedure for ketone synthesis. In this communication we wish to report a new one-pot procedure for the preparation of unsymmetrical ketones from 2-(6-(2-methoxyethyl)pyridyl) carboxylates (1a) and alkyl iodides by use of zinc dust and a catalytic amount of $NiCl_2$.

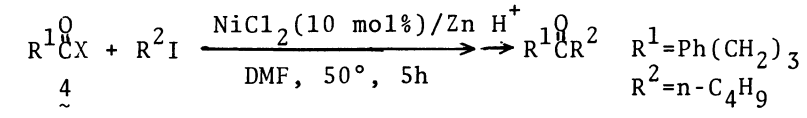


1a,b + 2 → 3

In the first place, we found that 2-pyridyl 4-phenylbutanoate (1b, $R^1=Ph(CH_2)_3$) reacts with 3 equiv. of butyl iodide[7] (2, $R^2=n\text{-}C_4H_9$) to give 1-phenyloctan-4-one in 62% yield in the presence of $NiCl_2$[8] (10 mol%) and zinc dust (3 equiv.) in N,N-dimethylformamide(DMF) at 50 °C. We examined the effect of the solvent, and found that use of DMF, N,N-dimethylacetamide, and N-methylpyrolidone gave similar results and that 1,4-dioxane showed much lower yield of the ketone than DMF and that use of hexamethylphosphoric triamide, pyridine and acetonitrile gave no or little ketone.

Next, we prepared various carboxylic acid derivatives such as acyl

Table 1. Reaction of R^1COX and R^2I[a)]



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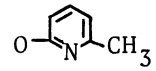
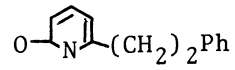
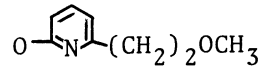
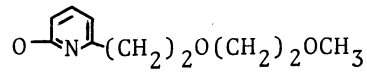
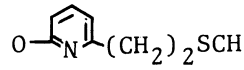
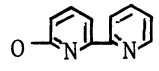
	X	Yield(%) of Ketone[b)]
a	Cl	0
b	SPh	0
c		46
d		62
e		75
f		75
g		87
h		75
i		81
j		35

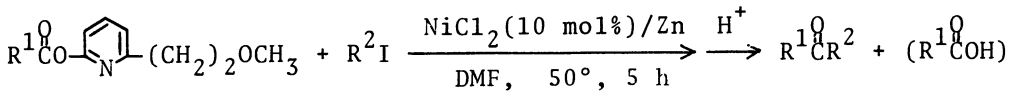
a) $R^1COX:R^2I:NiCl_2:Zn=1:3:0.1:3$

b) Yield was based on R^1COX.

chloride (4a), S-phenyl thioate (4b), S-(2-pyridyl) thioate (4c),[9)] and 2-(6-substituted pyridyl) carboxylates (4d~j),[10)] and compared the reactivities of them under the same reaction conditions as described previously. As shown in Table 1, use of 2-(6-(2-methoxyethyl)pyridyl) carboxylate (4g) gave the best yield of the ketone. We assume that the increase in the yield is attributed to the 2-methoxyethyl substituent which enables the 2-pyridyl ester to coordinate more tightly to the organometallic.

The results of the reactions of various 2-(6-(2-methoxyethyl)pyridyl) carboxylates with alkyl iodides are summarized in Table 2. A typical procedure for the preparation of 1-phenyloctan-4-one is as follows: To a mixture of anhydrous $NiCl_2$ (0.05 mmol) and zinc dust[11)] (1.5 mmol) was added a mixture of 2-(6-(2-methoxyethyl)pyridyl) 4-phenylbutanoate (0.5 mmol) and butyl iodide (1.5 mmol) in DMF (4 ml) under an argon atmosphere, and the mixture was stirred at 50 °C for 5 h. Then 2N HCl (10 ml) and ether (20 ml) were added. The ethereal layer was washed with 2N NaOH (20 ml) and H_2O (10 ml), dried, evaporated, and purified by chromatography (SiO_2) to give 1-phenyloctan-4-one in 87% yield. From

Table 2. Reaction of 2-(6-(2-methoxyethyl)pyridyl) carboxylates and alkyl iodides [a]



R^1	R^2	Yield(%)[b] Ketone[c]	(Recovered R^1COOH)
$Ph(CH_2)_3$	$n\text{-}C_4H_9$	87	(10)
	$Ph(CH_2)_4$[d]	85	(10)
	$n\text{-}C_6H_{13}CH(CH_3)$	83	(9)
	$t\text{-}C_4H_9$	0	(-)
	$CH_3OCO(CH_2)_3$	81	(5)
	$PhCO(CH_2)_3$	84	(10)
	$Cl(CH_2)_4$	85[e]	(9)
Ph	$n\text{-}C_4H_9$	99	(0)
$o\text{-}CH_3O\text{-}C_6H_4$	$n\text{-}C_4H_9$	91	(1)
$m\text{-}Cl\text{-}C_6H_4$	$n\text{-}C_4H_9$	81[e]	(8)
$C_2H_5OCO(CH_2)_4$	$n\text{-}C_4H_9$	86	(8)
$PhCO(CH_2)_4$	$n\text{-}C_4H_9$	72	(20)
$Cl\text{-}(CH_2)_3$	$Ph(CH_2)_4$[d]	81[e]	(-)
$n\text{-}C_3H_7CH(CH_3)$	$n\text{-}C_4H_9$	0 [44][f],12)	(71) [28][f]
PhCH=CH	$n\text{-}C_4H_9$	39[g]	(5)

a) 2-(6-(2-Methoxyethyl)pyridyl) carboxylate:R^2I:$NiCl_2$:Zn=1:3:0.1:3
b) Yields were based on 2-(6-(2-methoxyethyl)pyridyl) carboxylate.
c) All products showed satisfactory NMR and IR spectra.
d) Excess 4-phenylbutyl iodide was reduced to butylbenzene. No olefin was detected.
e) Reaction time is 1 h.
f) 2-Pyridyl ester was used instead of 2-(6-(2-methoxyethyl)pyridyl) ester.
g) Unidentified by-products were formed.

the alkaline water layer, 4-phenylbutanoic acid, which is supposed to be formed by hydrolysis of 2-(6-(2-methoxyethyl)pyridyl) 4-phenylbutanoate on work-up, was recovered in 10% yield.

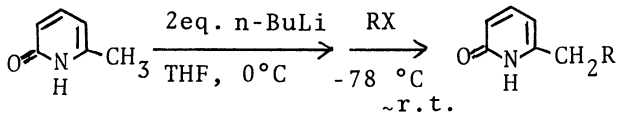
In preliminary experiments, we found that diethylzinc did not react with 2-(6-(2-methoxyethyl)pyridyl) 4-phenylbutanoate (4g) in DMF at 50 °C, and that treatment of diethylzinc with 4g in the presence of $NiCl_2$ (10 mol%) produced 6-phenylhexan-3-one in 36% yield. This indicates that the alkylnickel compound, formed from diethylzinc and $NiCl_2$, can react with 4g to give the ketone. It was also found that alkyl iodide did not react with zinc dust in DMF at 50 °C, but alkyl iodide was rapidly consumed in the presence of zinc dust and a catalytic amount of $NiCl_2$ in DMF at 50 °C. On the basis of these results, we assume that in the present reaction, an alkylnickel compound is initially formed from alkyl iodide and a low-valent nickel compound produced from $NiCl_2$ and zinc dust, and

that it in turn reacts with 2-(6-(2-methoxyethyl)pyridyl) carboxylate to give ketone and a nickel (II) compounds, which subsequently is reduced to a low-valent nickel compound by zinc dust and the catalytic cycle proceeds.

It is noted that the present reaction has several remarkable features: 1) By-products such as tertiary alcohol, which might be formed by further addition of R^2 group to the produced ketone, were scarecely obtained. 2) 2-(6-(2-Methoxyethyl)pyridyl) carboxylates and alkyl iodides having an active functional group such as a carbonyl group or a chlorine atom can be employed without protection as such. 3) The present method is a simple, one-pot procedure not requiring the preparation of organometallics beforehand. 4) The reaction proceeds under very mild and neutral conditions.

References and Notes

1) M. J. Jorgenson, Org. React., 18, 1 (1970).
2) G. H. Posner, Org. React., 22, 253 (1975).
3) C. R. Hauser, F. W. Swamer, and J. T. Adams, Org. React., 8, 59 (1954).
4) H. A. Staab and E. Jost, Justus Liebigs Ann. Chem., 655, 90 (1962); T. Sakan and Y. Mori, Chem. Lett., 1972, 793; K. Abe, T. Sato, N. Nakamura, and T. Sakan, Chem. Lett., 1977, 645; M. Araki, S. Sakata, H. Takei, and T. Mukaiyama, Chem. Lett., 1974, 687.
5) M. Araki, S. Sakata, H. Takei, and T. Mukaiyama, Bull. Chem. Soc. Jpn., 47, 1777 (1974).
6) M. Onaka, T. Goto, and T. Mukaiyama, Chem. Lett., 1979, 1483.
7) Only alkyl iodides were found to react.
8) No reaction occurred when $NiCl_2(P\ Ph_3)_2$ was used as a catalyst.
9) S-(2-Pyridyl) thioate was prepared according to the method in ref. 5).
10) 2-(6-Substituted pyridyl) carboxylates were all prepared from acyl chlorides and 6-substituted-2-pyridones in the presence of Et_3N in Et_2O at r.t. and purified by column chromatography (SiO_2) rapidly. 6-Substituted-2-pyridones except 4j were prepared from 6-methyl-2-pyridones according to the method in the literature: R. E. Smith, S. Boatman, and C. R. Hauser, J. Org. Chem., 33, 2083 (1968).



RX:	Yield
$PhCH_2Br$	44%
CH_3OCH_2Cl	38%
$CH_3OCH_2CH_2OCH_2Cl$	36%
CH_3SCH_2Cl	34%

6-(2-Pyridyl)-2-pyridone was prepared according to the method in the literature: T. Mukaiyama, F.-C. Pai, M. Onaka, and K. Narasaka, Chem. Lett., 1980, 563 (1980).
11) Org. Synth., Coll. Vol. III, 408 (1955).
12) In the case of secondary carboxylic acids, it is interesting to note that 2-pyridyl ester produces the corresponding ketone in a better yield than 2-(6-(2-methoxyethyl)pyridyl) ester.

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