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REGIOSELECTIVE SYNTHESIS OF 4-ALKYLPYRIDINES VIA 1, 4-DIHYDROPYRIDINE DERIVATIVES FROM PYRIDINE

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Abstract : N-Ethoxycarbonylpyridinium chloride (1) reacted with $RCu \cdot BF_3$ at 4-position with almost complete regioselectivity (better than 99%) to afford the corresponding 1, 4-dihydropyridine derivatives (2) in high yields (81 ~ 94%). The dihydropyridines were readily oxidized by oxygen to give 4-alkylpyridines (4 : 38 ~ 68% yields).

Many investigations have been reported on the reactions of organometallic reagents with pyridines to introduce substituents directly to pyridines.[1] For example, organolithiums[2] and Grignard reagents[2, 3] are shown to add preferably at 2-position of pyridine. Acylpyridinium salts are attacked mainly at 2-position by Grignard[4, 5] and organocadmium reagents[5] to give 2-substituted 1-acyl-1, 2-dihydropyridines. The only one organometallic reagent to attack 4-position of pyridinium salt predominantly is lithium dialkylcuprate, where only one half of the alkyl group of the reagent can be used.[6] Recently, Katritzky and co-workers reported the synthesis of 4-substituted pyridines in high yields, however, this method uses specially prepared pyridiniopyridones as the starting material[7] hence it is still desirable to device an efficient method to introduce substituents into 4-position of pyridine starting from pyridine itself.

In relation to this subject, recently we reported regiospecific synthesis of 4-alkylpyridines via alkylation of diisopropyl 1-ethoxycarbonyl-1, 4-dihydropyridine-4-phosphonate which is prepared directly from pyridine.[8] In order to develop a more convenient method for the synthesis of 4-alkylpyridines, we report here the reaction of various organometallic reagents with N-ethoxycarbonylpyridinium chloride (1). First we examined the reaction of 1 with butyllithium in ether, however, the corresponding dihydropyridine derivative was not obtained but the original pyridine was recovered. On the other hand, the reaction of 1 with $BuLi \cdot BBu_3$ in ether afforded a mixture of 1, 4- and 1, 2-dihydropyridine derivatives (2a : 3a = 75 : 25) in 42% yield. Also, $BuMgBr \cdot BBu_3$ attacked predominantly 4-position (2a : 3a = 62 : 38). However, as mentioned above,[4, 5] it is known that Grignard reagents react with 1 mainly at 2-position to give 1, 2-dihydropyridine derivatives. These

facts suggested that softer anions attacked 4-position more predominantly. Accordingly, we investigated the reaction of BuCu or BuCu·BF_3 with 1 and some of the results are summarized in Table 1. The exclusive attack at 4-position could be realized with BuCu or BuCu·BF_3 in high yields in THF (2a : 3a = ~99.5 : ~0.5), and when BuCu·BF_3 was used the yield was higher, compared with that using BuCu under the same conditions.

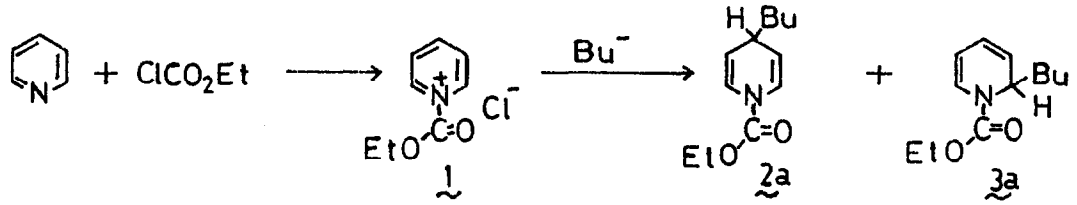

Table 1 Reaction of Various Organometallic Reagents with 1

Nucleophile		Yield of 2a and 3a (%)[3]	Ratio : 1, 4- (2a) / 1, 2- (3a)[4]	Solvent
BuLi		0	——	ether
BuLi·BBu_3[1]		42	75 / 25	ether
BuMgBr·BBu_3[1]		58	62 / 38	THF
BuCu	(BuLi + CuI)	35	——	ether
	(BuMgBr + CuI)	78	99.5 / 0.5	THF
BuCu·BF_3[2]	(BuLi + CuI)	48	98.0 / 2.0	ether
	(BuMgBr + CuI)	59	99.2 / 0.8	ether
	(BuMgBr + CuI)	89	99.5 / 0.5	THF

1) Tributylborane complex was prepared by addition of the borane to BuLi or BuMgBr at -78 °C. 2) This reagent was prepared following the procedure of Maruyama and Yamamoto.[9] 3) Isolated yield by Kugel-Rohr distillation.
4) Product ratio was determined by GLC analysis (5% Apiezon Grease L on Chromosorb WAW DMCS, 100 °C⟶230 °C).

Therefore, we examined the reaction of various RCu·BF_3 with 1 in THF and some of the results are summarized in Table 2. Evidently this method is superior to that with lithium dialkylcuprate,[6] because one equivalent of an alkyl group is transferred to the pyridine nucleus stoichiometrically. Moreover, the ratio (99.0 : 1.0) is kept high enough even with PhCu·BF_3, where it is lowered to 90 : 10 with lithium diphenylcuprate.

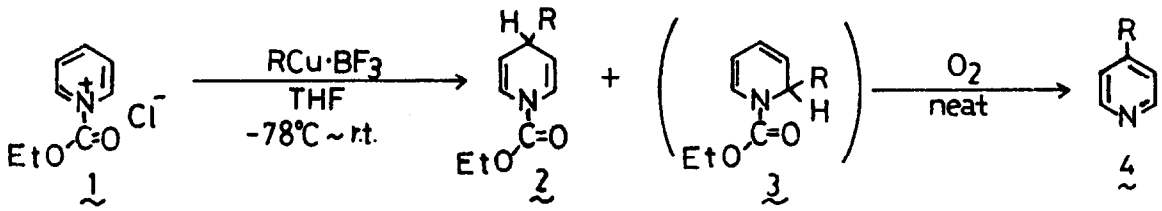

Table 2 Regioselective Synthesis of 2 and 4

	R	Total Yield of 2 and 3[1] (%)	Ratio : 1, 4- (2) / 1, 2- (3)[2]	Oxidation Time (h)	Yield of 4[3] (%)
a	$CH_3(CH_2)_3$-	89	99.5 / 0.5	6.5	68
b	$CH_3(CH_2)_5$-	85	99.7 / 0.3	1	66
c	$PhCH_2CH_2$-	81	100 / 0	19	55
d	$CH_3CH_2(CH_3)CH$-	83	99.7 / 0.3	7	38
e	Ph-	94	99.0 / 1.0	12	59

1) Isolated yield by Kugel-Rohr distillation. Satisfactory IR and ^{1}H NMR data were obtained for these compounds and satisfactory MS data was obtained for 2a. 2) By GLC analysis (5% Apiezon Grease L on Chromosorb WAW DMCS, 100 °C→230 °C). 3) Isolated yield by Kugel-Rohr distillation. Identified by IR and ^{1}H NMR spectroscopy and MS.

The final stage of the synthesis of 4-alkylpyridines (4) is oxidation of 1, 4-dihydropyridine derivatives (2), on which nothing is described in the corresponding literature.[6] When 2 was allowed to stir without solvent under a stream of oxygen, 4 was easily obtained and the results are summarized in Table 2.

The following procedure for the synthesis of 4-butylpyridine (4a) is representative. In a 250 ml flask, were placed CuI (3.36 g, 17.6 mmol) and dry THF (60 ml). BuMgBr prepared from butylbromide (1.90 ml, 17.6 mmol) and magnesium (0.43 g, 17.6 mmol) in THF was added at -20 °C under nitrogen through a double-ended needle and the mixture was stirred for 30 min at this temperature. Then the mixture was cooled to -78 °C and $BF_3 \cdot OEt_2$ (2.17 ml, 17.6 mmol) was added slowly. After stirring for 10 min at -78 °C, the resulting brown mixture was transferred through a double-ended needle to the suspension of 1 prepared from pyridine (1.22 ml, 15.0 mmol) and ethyl chloroformate (1.44 ml, 15.0 mmol) in THF (60 ml), and the mixture was allowed to warm slowly to room temperature with stirring. The color changed from brown to dark gray. After the reaction mixture was stirred for 3h at room temperature, aqueous 5% $NaHCO_3$ (100 ml) was added and the

THF was evaporated under reduced pressure. The product was extracted with ether (30 ml × 3) and the solvent was evaporated in vacuo after being dried over anhydrous $MgSO_4$. The crude product was purified by Kugel-Rohr distillation to afford 2a (2.80 g) in 89% yield. b.p. 120 - 140 °C / 1 mmHg (temperature of Kugel-Rohr distillation). ^1H NMR ($CDCl_3$) : δ 0.6 ~ 1.5 (m, 12H), 2.91 (m, 1H), 4.19 (q, 2H, J=7 Hz), 4.77 (dd, 2H, J=8, 3 Hz), 6.79 (broad d, 2H, J=8 Hz). IR (neat) : 1720, 1690, 1635, 1415, 1400, 1375, 1335, 1310, 1210, 1120, 970, 950, 760, 740 cm^{-1}. MS (m / e) ; 209 (M^+). In the next, 2a (0.338 g, 1.62 mmol) was placed in a flask and stirred for 6.5h under a stream of oxygen. Aqueous 5N HCl was added into the mixture until a pH of 2 was obtained and the water layer was extracted with CH_2Cl_2 (20 ml × 2). The extracts were discarded, and the acidic solution was treated with aqueous 3N NaOH until a pH of 11 was obtained. Then the product was extracted with CH_2Cl_2 (50 ml × 2) and the combined extracts were dried over anhydrous $MgSO_4$, filtered, concentrated on a rotary evaporator, and distilled by Kugel-Rohr to give 0.149 g (68%) of 4-butylpyridine (4a). b.p. 90 ~ 110 °C / 12 mmHg (temperature of Kugel-Rohr distillation, lit. 98 °C / 20 mmHg[10]).

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