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REGIOSPECIFIC INTRODUCTION OF ALKYL GROUPS INTO 4-POSITION OF PYRIDINE NOVEL SYNTHESIS OF 4-SUBSTITUTED PYRIDINES

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Abstract : Regiospecific synthesis of 4-substituted pyridines is attained via alkylation of diisopropyl 1-ethoxycarbonyl-1, 4-dihydropyridine-4-phosphonate followed by treatment with butyllithium. The phosphonate is prepared directly from pyridine in one pot.

Considerable efforts have been made to introduce substituents directly to pyridine and Grignard reagents and organolithiums are shown to add at 2-position to afford 2-substituted pyridines after air oxidation.[1] 3-Substituted pyridines are also prepared by alkylation of 1, 2-dihydropyridine generated in situ from pyridine and lithium aluminum hydride.[2] Acylpyridinium salts are attacked mainly at 2-position by Grignard reagents[3, 4] and phenylcadmiums[4] to give 1-acyl-1, 2-dihydropyridines, but there is only one exception of the reaction with cuprates.[5] However, most of them have not been converted to substituted pyridines. Katritzky et al. are the only one group, to our knowledge, who reported the synthesis of 4-substituted pyridines in high yields, however, this method uses specially prepared pyridiniopyridones as the starting material[6] hence it is still desirable to device a method to introduce substituents into 4-position of pyridine starting from pyridine itself.

We wish to report here a novel method for specific introduction of alkyl groups to 4-position of pyridine as an extention of our efforts to develop new versatile methods to introduce substituents into heterocycles starting from heteroaromatic cations.[7]

First we tried to prepare 1, 2- (3) or 1, 4-dihydropyridinephosphonate (4) selectively and then to use them for carbonyl olefination to obtain the corresponding exo-methylene compounds. 2, 6-Di-t-butyl-4-methylphenyl chloroformate (1a) was chosen as an acylating reagent to block 2, 6-positions of the resulting pyridinium salt (2a) sterically against the attack of trimethyl phosphite to obtain the 4-phosphonate (4a) predominantly. However, almost 1 : 1 mixture of 3a and 4a was obtained and essentially the same result was realized when ethyl chloroformate was used instead of 1a. Therefore, we changed the alkyl group of phosphite as the origin of steric hindrance for 2, 6-positions, and finally succeeded to prepare diisopropyl 1-ethoxycarbonyl-1, 4-dihydropyridine-4-phosphonate (4d)

regioselectively in a good yield. The presence of 2-phosphonate (3d) was not detected by ^{1}H NMR, TLC and GLC. Satisfactory elemental analyses were obtained for 4d and spectral data are shown.

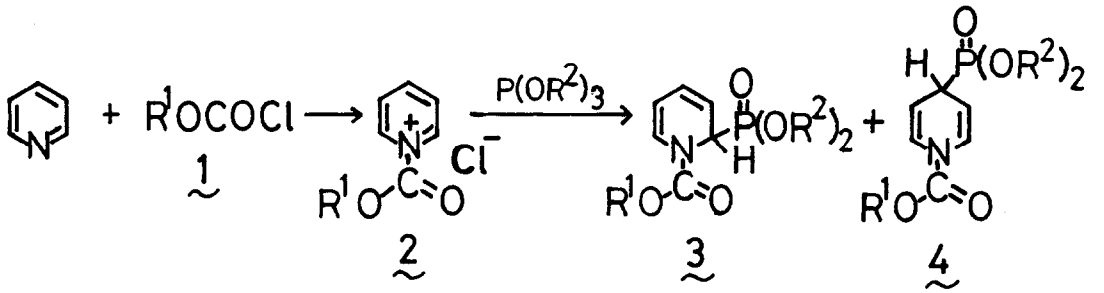


Table 1 Yields and Ratio of Dihydropyridinephosphonates

	R^1	R^2	Yield (%) 3 + 4	bp °C/mmHg	Ratio 3 : 4
a:	2,6-di-t-Bu-4-Me-C_6H_2	Me	43	oil	49 : 51
b:	Et	Me	55	135/0.9	46 : 54
c:	Et	Et	70	130/0.25	8 : 92
d:	Et	i-Pr	73	129/0.25	0 : 100

Spectral data of 4d, ^{1}H NMR (CCl_4) : δ 1.28 (d, 12H, J=6.0 Hz), 1.32 (t, 3H, J=6.5 Hz), 3.27 (br. d, 1H, J=30 Hz), 4.22 (q, 2H, J=6.5 Hz), 4.33 - 5.05 (m, 4H), 6.50 - 7.00 (m, 2H). MS (m / e) : 317 (M^+, 1%), 152 (M^+-P(O)(O-i-Pr)$_2$, 100), 80 (py^+ + H, 81).

When 4d was treated with an equimolar amount of butyllithium in tetrahydrofuran at -78 °C under nitrogen and quenched with deuteroxide, the corresponding 4-deuterated compound was recovered quantitatively. Hence, alkylation of the anion thus generated was tried with several alkyl halides, and afforded the expected diisopropyl 4-alkyl-1-ethoxycarbonyl-1, 4-dihydropyridine-4-phosphonates (5) in high yields as shown in Table 2.

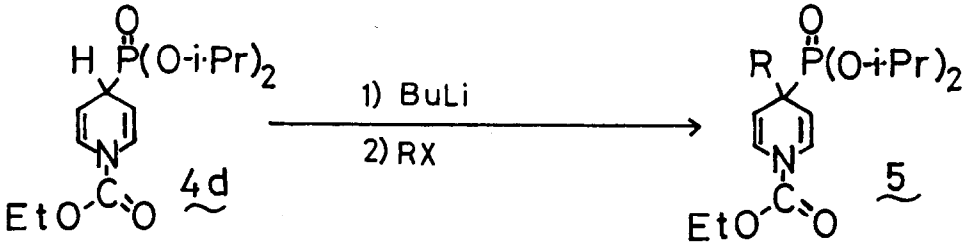


Table 2 Yields of 4-Alkyl-1, 4-dihydropyridine-4-phosphonates

5	RX	Yield (%)	bp (°C)[1]
a:	CH_3I	74	170-190/0.2[2]
b:	C_2H_5Br	76	180/0.2[3]
c:	CH_2=$CHCH_2Br$	70	170-200/0.25
d:	C_4H_9Br	78	190-205/0.3
e:	$C_6H_5CH_2Br$	87	210-240/0.17

1) Temperature of Kugel-Rohr distillation

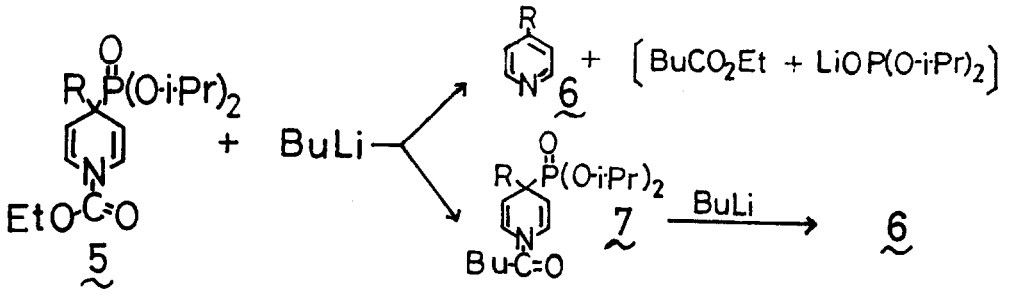
2) Boiling point of second Kugel-Rohr distillation was 175 °C / 0.2 mmHg.

3) Purified by flash column chromatography (SiO_2, Et_2O : AcOEt = 7 : 3) before distillation

4) All 5 are hygroscopic. 5c and 5d gave correct elemental analyses, but 5a, b, e gave correct result only when ca. 0.2 mole of water is assumed to be contained.

The final stage of the synthesis of 4-alkylpyridines is elimination of the ethoxycarbonyl and the phosphonyl groups. This was tried by a couple of procedures. When 5d and 5e were heated in HMPT at 150 - 160 °C for 2 - 3 h in the presence of 5 equivalents of sodium iodide, 4-butyl- and 4-benzylpyridines were obtained in 48 and 44% yields after Kugel-Rohr distillation. When 5c was treated as above, 4-(1-propenyl) pyridine was obtained in 21% yield, hence isomerization of the double bond occurred during the heating. When 5d was treated in methanol in the presence of lithium methoxide, only ester exchange took place to give the corresponding methyl ester almost quantitatively, thus elimination was not observed.

However, 4-butylpyridine (6d) was obtained in 86% yield after column chromatography (alumina, ether as an eluent), when hexane solution (15 ml) of 5d (5.47 mM) was treated with ca. two equivalents of butyllithium (11.0 mM in 7.30 ml of hexane) at zero to room temperature for 1 h. A small amount of diisopropyl 4-butyl-1-valeroyl-1, 4-dihydropyridine-4-phosphonate (7d : 7%) was also isolated together with 6d. This was supported by the fact that almost 1 : 1 mixture of 6d and 7d was obtained by similar treatment of 5d with an equimolar amount of butyllithium. These facts suggest that there is a competition to afford 6 and 7 when butyllithium attacks the ethoxycarbonyl group, and then 7 is again attacked by butyllithium to give 6 and there are a couple of side reactions to consume extra butyllithium.



Hence we have presented a novel and versatile method for synthesis of 4-alkylpyridines starting from pyridine itself. The key idea here is to introduce the phosphonyl group regioselectively at 4-position and to use the same group as the anion stabilizing group and also as the leaving group in a regiospecific way.

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References

1) U. Eisner and J. Kuthan, Chem. Rev., 72, 1 (1972).
W. von E. Doering and V. Z. Pasternak, J. Am. Chem. Soc., 72, 143 (1950).
C. S. Giam, E. E. Knaus, and F. M. Pasutto, J. Org. Chem., 39, 3565, (1974).
C. S. Giam and J. L. Stout, J. C. S. Chem. Commun., 1970, 478.
2) C. S. Giam and S. D. Abott, J. Am. Chem. Soc., 93, 1294 (1971).
3) G. Frankel, J. W. Cooper, and C. M. Fink, Angew. Chem. Intern. Ed., 9, 523 (1970).
4) R. E. Lyle, J. L. Marshall, and D. L. Comins, Tetrahedron Lett., 1977, 1015.
5) E. Piers and M. Soucy, Can. J. Chem., 52, 3563 (1974).
6) A. R. Katritzky, H. Beltrami, and M. P. Sammes, J.C. S. Chem. Commun., 1979, 137.
A. R. Katritzky, H. Beltrami, J. G. Keay, D. N. Rogers, M. P. Sammes, C. W. G. Leung, and C. M. Lee, Angew. Chem. Intern. Ed., 18, 792 (1979).
A. R. Katritzky, J. G. Keay, and M. P. Sammes, J. C. S. Perkin I, 1981, 668.
7) K. Ishikawa, K. Akiba, and N. Inamoto, Tetrahedron Lett., 1976, 3695.
K. Akiba, K. Ishikawa, and N. Inamoto, Bull. Chem. Soc. Jpn., 51, 2674 (1978).
K. Ishikawa, K. Akiba, and N. Inamoto, ibid, 51, 2684 (1978).
K. Akiba, Y. Negishi, and N. Inamoto, Synthesis, 1979, 55.

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