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REGIOSELECTIVE SYNTHESIS OF 4-ALKYLPYRIDINES FROM PYRIDINE AND ALDEHYDES VIA DIPOLE REVERSAL PROCESS OF 1,4-DIHYDROPYRIDINE PHOSPHONATE[†]

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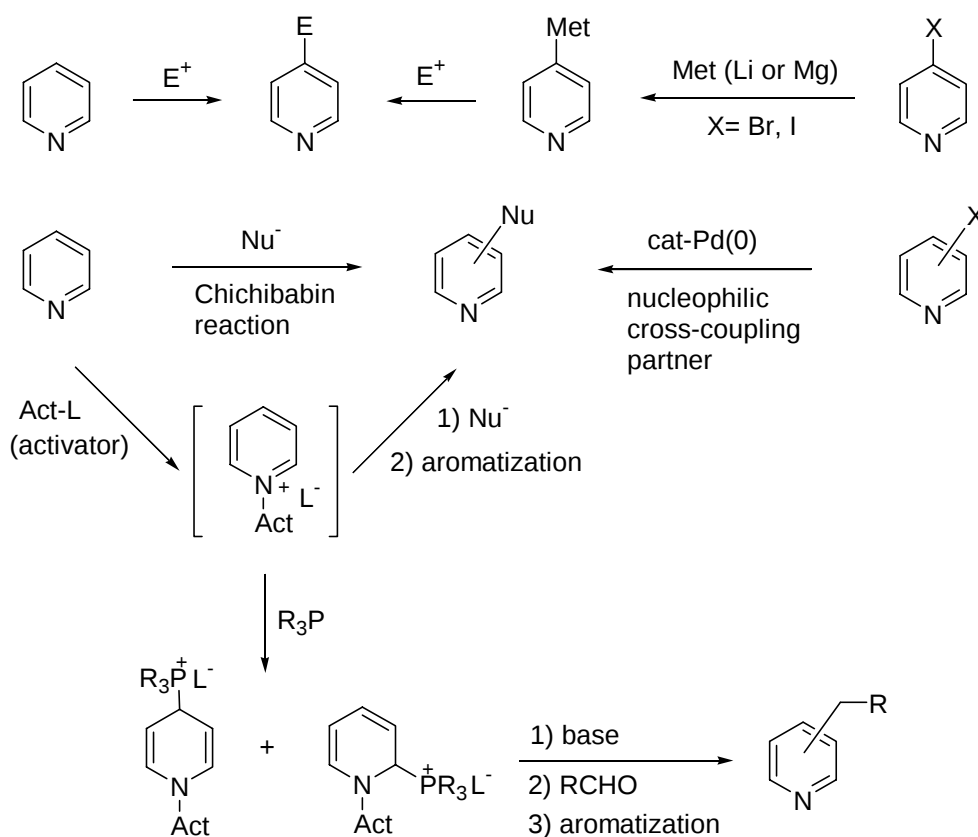
[†]This paper is dedicated for the 65th birthday of Professor Barry M. Trost.

Abstract – 4-Alkylation of pyridine has been accomplished by the reaction of ylides, derivated from 1,4-dihydropyridine phosphonate *via* phosphonioalkoxy-carbonylation of pyridine with aldehydes and subsequent elimination of diisopropyl phosphate followed by aromatization with potassium *tert*-butoxide.

INTRODUCTION

Functionalization of pyridines constitutes a powerful method for the synthesis of natural products and biologically active compounds.¹ Regioselective introduction of a variety of functional groups on a pyridine ring has attracted considerable attention.² Because pyridine undergoes electrophilic aromatic substitution only under extreme conditions, introduction of a variety of electrophiles on pyridine was accomplished mainly by the reaction of electrophiles with carbanions obtained from metal-halogen exchange reaction in halopyridine.³ On the other hand, pyridine undergoes nucleophilic substitution much more readily than does benzene due to relatively electron deficiency of the pyridine.⁴ Therefore, introduction of nucleophiles on a pyridine was achieved by metal-catalyzed cross-coupling reaction of halopyridines⁵ or the Chichibabin reaction.⁴ Although direct introduction of nucleophiles on pyridines has been successful, activation of the pyridine ring was required sometimes for mild reaction conditions.⁶ In addition, the functionalization of pyridines can be normally accomplished by dipole reversal process, namely, the conversion of pyridines into adducts which serve as pyridine anion equivalents.⁷ These approaches consist of the introduction of suitable functional groups at 2 or 4-position of pyridine, which is capable of generating stable anions at 2 or 4-position as well as being easily eliminated to regenerate double bonds. Although examination of the literature indicates that a number of different synthetic

methods have been developed, one of the promising methods involves phosphonio-alkoxycarbonylation of pyridines. In this paper, we report that 4-alkylpyridines can be prepared from pyridine and a variety of aldehydes *via* dipole reversal process (Scheme 1).



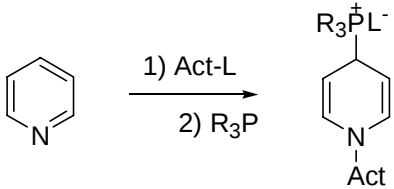
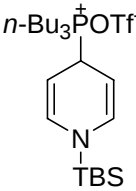
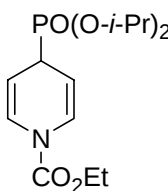
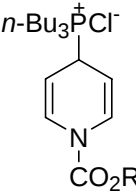
Scheme 1.

RESULTS AND DISCUSSION

To find optimum conditions for the synthesis of 4-alkylpyridines from pyridine and aldehydes *via* dipole reversal process, a variety of trivalent phosphorus compounds were examined. Because the addition reactions of $n-Bu_3P$, Ph_3P , and $(i-PrO)_3P$ to pyridine did not proceed directly, increase of electrophilicity of pyridine was needed and then, a variety of activators were tested. The results are summarized in Table 1. Reaction of pyridine with TBDMSCl in THF gave *N*-TBDMS pyridinium chloride in *ca.* 15% yield. Moreover, treatment of *N*-TBDMS pyridinium chloride with $n-Bu_3P$, Ph_3P , and $(i-PrO)_3P$, respectively, regenerated pyridine *via* desilylation (entries 1-3). Although the pyridinium salt obtained quantitatively from pyridine and TBDMSOTf did not react with Ph_3P or $(i-PrO)_3P$ (entries 5 and 6), $n-Bu_3P$ reacted with salt to afford product (**1**) in 20% yield (entry 4). Subjecting pyridine activated with methyl chloroformate to $n-Bu_3P$ produced regioselectively the desired addition product (**2**) in 99% yield (entry 7). In the case of ethyl chloroformate as an activator, *N*-ethoxycarbonylpyridinium chloride reacted with $n-Bu_3P$ to furnish the 1,4-addition products (**3**) in 98% yield (entry 9). When $(i-PrO)_3P$ and NaI were used, **4** was produced

in 91% yield (entry 10). *N*-Phenoxycarbonylpyridinium chloride did not react with Ph_3P while treatment of salt with *n*- Bu_3P provided the desired product (**5**) (entries 11 and 12).

Table 1. Optimization of the reaction of pyridine with $\text{R}_3\text{P}^{\text{a}}$

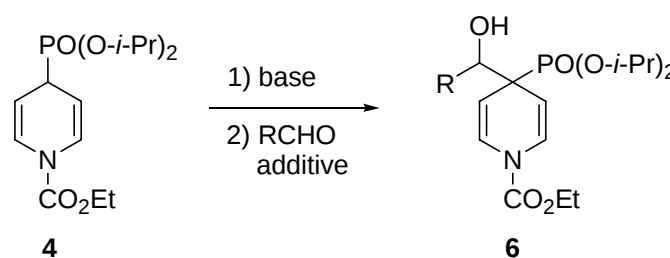
						
entry	Act-L	R_3P	product	yield (%) ^b		
1	TBDMSCl	<i>n</i> - Bu_3P		0	 1	 4
2	TBDMSCl	Ph_3P		0		
3	TBDMSCl	(<i>i</i> -PrO) $_3\text{P}$		0		
4	TBDMSOTf	<i>n</i> - Bu_3P	1	20		
5	TBDMSOTf	Ph_3P		0		
6	TBDMSOTf	(<i>i</i> -PrO) $_3\text{P}$		0		
7	MeOCOCi	<i>n</i> - Bu_3P	2	99	 $\text{R} = \text{Me}$ 2 Et 3 Ph 5	
8	MeOCOCi	Ph_3P		0		
9	EtOCOCi	<i>n</i> - Bu_3P	3	98		
10 ^c	EtOCOCi	(<i>i</i> -PrO) $_3\text{P}$	4	91(51) ^d		
11	PhOCOCi	<i>n</i> - Bu_3P	5	98		
12	PhOCOCi	Ph_3P		0		

^a1 Equiv. of Pyridine, 1.06 equiv. of Act-L, and 1.06 equiv. of R_3P were used. ^bNMR spectral yields obtained on the basis of an internal standard (4-methylanisole). ^c1.1 Equiv. of NaI was used. ^dIsolated yield by Kugel-Rohr distillation.

On the basis of these results, hydroxyalkylation of dihydropyridine tributylphosphonium salt (**2**, **3**, and **5**) or phosphonate (**4**) was scrutinized. The results are summarized in Table 2. After **2** or **5** were treated with NaH, LDA, and *n*-BuLi, addition of a variety of aldehydes to the red-brown ylide did not produce the any olefin product or 4-benzylpyridine, in spite of use of HMPA as a cosolvent (entries 1, 2, and 3). In addition, reaction of the ylide with excess methyl iodide did not afford the desired products even at 70 °C. These imply that nucleophilicity of the corresponding ylide might be too weak to attack electrophiles such as benzaldehyde and methyl iodide due to alkoxycarbonyl group which is strong electron-withdrawing group. Encouraged by these results, dihydropyridinephosphonate (**4**) was treated with *n*-BuLi followed by benzaldehyde to give the desired product (**6a**) in 48% yield (entry 6). The use of additive such as TMSOTf and BF_3OEt_2 afforded **6a** in 40% and 51% yields, respectively (entries 4 and 5). The best results were obtained with 1.2 equiv. of LDA and 1.2 equiv. of benzaldehyde without additive in THF at 50 °C

for 2 h, producing the corresponding compound (**6a**) in 68% yield (entry 9). To demonstrate the efficiency and scope of the present methods, we applied the optimum conditions to a variety of alkyl- and arylaldehydes. Butyraldehyde and isobutyraldehyde provided **6b** and **6d** in 64% and 64% yield, respectively (entries 10 and 12). Treatment of the ylide generated from **4** and LDA with 2-methylbenzaldehyde and 4-chlorobenzaldehyde furnished the desired products (**6e**) and (**6i**) in 62% and

Table 2. Hydroxyalkylation of dihydropyridine phosphonate^a

					
entry	base	R	additive	product	yield (%) ^b
1	NaH	Ph		6a	0 ^c
2	LDA	Ph		6a	0 ^c
3	<i>n</i> -BuLi	Ph		6a	0 ^c
4	<i>n</i> -BuLi	Ph	TMSOTf	6a	40
5	<i>n</i> -BuLi	Ph	BF ₃ OEt ₂	6a	51
6	<i>n</i> -BuLi	Ph		6a	48
7	LDA	Ph	TMSOTf	6a	42
8	LDA	Ph	BF ₃ OEt ₂	6a	55
9	LDA	Ph		6a	68
10	LDA	<i>n</i> -Pr		6b	64
11	LDA	Me(CH ₂) ₆ CH ₂		6c	41
12	LDA	<i>i</i> -Pr		6d	64
13	LDA	2-Me-C ₆ H ₄		6e	62
14	LDA	2-NO ₂ -C ₆ H ₄		6f	65
15	LDA	3-Br-C ₆ H ₄		6g	54
16	LDA	4-Me-C ₆ H ₄		6h	74
17	LDA	4-Cl-C ₆ H ₄		6i	65
18	LDA	4-MeO-C ₆ H ₄		6j	22
19	LDA	2-C ₄ H ₃ O ^d		6k	46
20	LDA	2-C ₄ H ₃ S ^e		6l	26
21	LDA	MeCH=CH		6m	62
22	LDA	Me(CH ₂) ₅ CH=CH		6n	58

^a1 Equiv. of **4**, 1.2 equiv. of base, 1.2 equiv. of additive, and 1.2 equiv. of RCHO were used. ^bIsolated yield. ^c**2** or **5** were used instead of **4**. HMPA was used as a cosolvent. ^d2-Furaldehyde. ^e2-Thiophenecarboxaldehyde.

65% yields, respectively (entries 13 and 17). Electronic variation on the aromatic substituents diminished the efficiency of hydroxyalkylation. The desired product was obtained in low yield (22%) in the case of 4-methoxybenzaldehyde (entry 18). 2-Furaldehyde turned out to be compatible with the employed reaction conditions (entry 19). Reaction of **4** with 2-thiophenecarboxaldehyde gave the desired product in 26% yield due to instability of the starting material (entry 20). Exposure of the ylide to α,β -unsaturated aldehydes such as *trans*-crotonaldehyde and *trans*-2-nonenal gave the products (**6m**) and (**6n**) in good yields (entries 21 and 22).

Finally, a variety of hydroxyalkylated compounds (**6**) were treated with 1.2 equiv. of potassium *tert*-butoxide in THF to produce 4-alkylpyridines (**7**) via olefination followed by aromatization. The results are summarized in Table 3. Treatment of **4** with 2 equiv. of LDA followed by benzaldehyde afforded 4-benzylpyridine in 32% yield, which was produced by hydroxybenzylation and rearomatization. Although **6m** and **6n** could not give the corresponding pyridines under the present conditions (entries 12 and 13), hydroxyalkylated compounds (**6a** ~ **6k**) derived from aromatic and aliphatic aldehydes afforded

Table 3. Synthesis of 4-alkylpyridine via olefination followed by aromatization^a

Reaction scheme: **6** (with R group) $\xrightarrow[\text{THF}]{\text{tert-BuOK}}$ **7** (with R group)

entry	R	product	yield (%) ^b
1	<i>n</i> -Pr	7b	55
2	Me(CH ₂) ₆ CH ₂	7c	87
3	<i>i</i> -Pr	7d	63
4	Ph	7a	69
5	2-Me-C ₆ H ₄	7e	73
6	2-NO ₂ -C ₆ H ₄	7f	68
7	3-Br-C ₆ H ₄	7g	67
8	4-Me-C ₆ H ₄	7h	50
9	4-Cl-C ₆ H ₄	7i	61
10	4-Ac-C ₆ H ₄	7j	64
11	2-C ₄ H ₃ O ^c	7k	54
12	MeCH=CH	7l	0
13	Me(CH ₂) ₅ CH=CH	7m	0

^a1 Equiv. of **6** and 1.2 equiv. of potassium *tert*-butoxide in THF were used. ^bIsolated yield. ^c2-Furaldehyde.

the 4-alkylpyridines in good yields (50 ~ 87%, entries 1~11).

In conclusion, this study has led to the development of regioselective synthetic methods of 4-alkylpyridines from pyridine and aldehydes. Pyridinium salts activated by methyl, ethyl, or phenyl chloroformate reacted with *n*-Bu₃P and (*i*-PrO)₃P to produce 1,4-dihydropyridinephosphorus compounds, which were converted to 4-alkylpyridines in good yields *via* olefination followed by aromatization with potassium *tert*-butoxide. The present method complements existing methods as a result of regioselective introduction of alkyl groups to C4-position of pyridine *via* dipole reversal process.

EXPERIMENTAL

General: Reactions were carried out in oven-dried glassware under nitrogen atmosphere. All commercial reagents were used without purification, and all solvents were reaction grade. THF was fresh distilled from sodium/benzophenone under nitrogen. All reaction mixtures were stirred magnetically and were monitored by TLC using Merck silica gel 60 F₂₅₄ precoated glass plates, which were visualized with UV light, and then, developed by using Fluka silica gel 60 (0.040-0.063 mm, 230-400 mesh). ¹H NMR and ¹³C NMR spectra were recorded on Bruker DPX FT (400 MHz) spectrometer. Deuterated chloroform was used as the solvent, and chemical shifts (δ) are reported in parts per million relative to the residual signals of this solvent (δ 7.24 for ¹H and δ 77.0 for ¹³C). HRMS spectra were recorded on a VG Autospec Ulpima. IR spectra were recorded on a JASCO FT/IR-460 plus FT-IR spectrometer as either a thin film pressed between two sodium chloride plates or as a solid suspended in a potassium bromide disk.

Diisopropyl 1-ethoxycarbonyl-1,4-dihydropyridine-4-phosphonate (4).

To a solution of pyridine (395.5 mg, 5.0 mmol) in MeCN (15 mL) was added ethyl chloroformate (542.6 mg, 5.0 mmol) at 0 °C. After 30 min, triisopropyl phosphite (1.04 g, 5.0 mmol) and sodium iodide (824.4 mg, 5.5 mmol) were added. The reaction mixture was warmed to 50 °C and stirred for 2 h. The reaction mixture was concentrated under reduced pressure and the residue was diluted with CH₂Cl₂. The organic layers were washed with NH₄Cl (sat. aq. 20 mL) and brine (20 mL), the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL), and combined organics dried with MgSO₄, filtered, and concentrated under reduced pressure. The crude material was purified by Kugel-Rohr distillation (bp 120 °C /0.4 mmHg) to give **4** (809.2 mg, 51%) as a clear colorless liquid. ¹H NMR (400 MHz, CDCl₃) δ 6.85 (br d, 2H), 4.94 (br d, 2H), 4.25 (q, *J* = 7.2 Hz, 2H), 3.47-3.39 (m, 3H), 1.40-1.25 (m, 15H); ¹³C NMR (100 MHz, CDCl₃) δ 151.5, 125.7, 102.4, 71.3, 63.1, 34.8, 24.4, 14.8; IR (film) 3284, 2960, 1684 cm⁻¹; HRMS (EI) calcd for C₁₄H₂₄NO₅P (M⁺) 317.1392, found 317.1395.

Diisopropyl 1-ethoxycarbonyl-4-(1'-hydroxybenzyl)-1,4-dihydropyridine-4-phosphonate (6a).

To a solution of diisopropyl 1-ethoxycarbonyl-1,4-dihydropyridine-4-phosphonate (**4**) (772.0 mg, 2.43 mmol) in THF (5 mL) was added LDA which was generated from the reaction of diisopropylamine

(295.5 mg, 2.92 mmol) and *n*-BuLi (1.55 M in hexane, 2.92 mmol) in THF (3 mL) at -78 °C for 15 min. The solution was stirred at -78 °C for 1 h and then, benzaldehyde (309.8 mg, 2.92 mmol) was added to reaction mixture. After 80 min, the reaction mixture was quenched with NH₄Cl (sat. aq. 6 mL). The aqueous layer was extracted with ether (3 x 20 mL), and combined organics were washed with NH₄Cl (sat. aq. 20 mL) and brine (20 mL), dried with MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexane = 2/3) to give **6a** (703.0 mg, 68%) as an oil. ¹H NMR (200 MHz, CDCl₃) 7.40-7.19 (m, 5H), 6.87 (br d, 1H), 6.59 (br d, 1H), 5.29 (br s, 1H), 4.96 (d, *J* = 8.2 Hz, 1H), 4.88-4.52 (m, 4H), 4.14 (q, *J* = 6.8 Hz, 2H), 1.41-1.19 (m, 15 H); ¹³C NMR (100 MHz, CDCl₃) δ 151.5, 140.9, 128.7, 127.4, 127.3, 125.5, 102.4, 72.1, 63.1, 36.1, 14.8; IR (film) 3360, 1730, 1695 cm⁻¹; HRMS (EI) calcd for C₂₁H₃₀NO₆P (M⁺) 423.1811, found 423.1814.

4-Benzylpyridine (7a).

Potassium *tert*-butoxide (76.4 mg, 0.68 mmol) was added to a solution of **6a** (240.0 mg, 0.57 mmol) in THF (5 mL). After 30 min, the reaction mixture was quenched with NaCl (sat. aq. 5 mL). The aqueous layer was extracted with ether (3 x 20 mL), and combined organics were washed with NaCl (sat. aq. 20 mL) and dried with MgSO₄, filtered, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (EtOAc/Hexane = 2/3) to give **7a** (59.4 mg, 62%) as an oil. ¹H NMR (400 MHz, CDCl₃) 8.50 (d, *J* = 6.9 Hz, 2H), 7.37-7.10 (m, 7H), 3.98 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) δ 141.0, 128.8, 127.2, 127.0, 125.0, 102.0, 72.1, 71.0, 54.1, 34.5, 23.9, 14.0; IR (film) 1630, 1423, 1267 cm⁻¹; HRMS (EI) calcd for C₁₂H₁₁N (M⁺) 169.0891, found 169.0893.

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