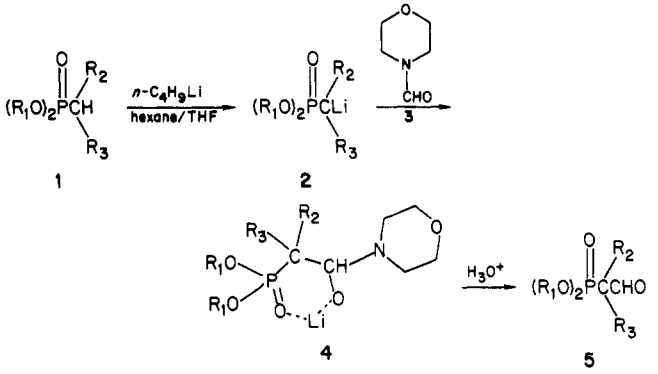
Table II. Preparation of Dialkyl (1-Formylalkyl)phosphonates 5

R_1	R_2	R_3	yield, present run	yield, reported[6]	bp [°C/mmHg], found	bp [°C/mmHg], lit.[6]
C_2H_5	H	H	85	53	72–76/0.25	76–79/0.3
i-C_3H_7	H	H	83	51	72–78/0.5	94–98/2
C_2H_5	CH_3	H	94	86	93–5/2	93–96/2
i-C_3H_7	CH_3	H	91	88	80–85/1	98–102/2
C_2H_5	CH_3	CH_3	83	79	98–100/4	88–91/2
C_2H_5	C_2H_5	H	80	78	98–102/2.8	96–99/2

[a] Yields of dialkyl (1-formylalkyl)phosphonates refer to isolated (distilled) products; they gave ^1H NMR and ^{31}P NMR spectra which were identical with those of the reported[6] compounds.

an attractive one complementing previously reported methods.



Experimental Section

A. General Procedure for the Formylation of Grignard Reagents with *N*-Formylmorpholine. To a stirred solution of freshly prepared Grignard reagent (10 mmol) in dry diethyl ether (20 mL), cooled to 0 °C, is slowly added during 2 min a solution of *N*-formylmorpholine (Aldrich) (10 mmol) in diethyl ether (10 mL). An exothermic reaction takes place. The reaction mixture is stirred for another 30 min at room temperature and then quenched with 3 N HCl until the solution becomes completely acidic (pH2). The product is extracted with diethyl ether, washed twice with water, and then with saturated sodium hydrogen carbonate and saturated sodium chloride solutions. The organic layers are combined and dried over anhydrous sodium sulfate. Removal of the solvent gives the corresponding aldehyde in almost pure form.[8] Further purification by either distillation or crystallization furnished pure products which were characterized by their bp, IR, NMR, and TLC.

B. General Procedure for the Formylation of Organolithium Compounds with *N*-Formylmorpholine. To a 0 °C solution of freshly prepared organolithium compound (10 mmol) in the appropriate solvent (see Table I) (10 mL) is added during 2 min a solution of *N*-formylmorpholine (10 mmol) in the same solvent (15 mL). The reaction is moderately exothermic. The solution is allowed to stir for an additional 30 min and then worked up following the procedure described above.[8]

C. General Procedure for the Formylation of Dialkyl Alkylphosphonates with *N*-Formylmorpholine. To a solution of 12 mmol (2.7 M) of *n*-butyllithium in tetrahydrofuran under N_2 at −78 °C is added during 2 min a solution of the dialkyl alkylphosphonate (10 mmol) in 10 mL of tetrahydrofuran. After stirring for 10 min, a solution of *N*-formylmorpholine (12 mmol) in 10 mL of THF is added. The mixture was allowed to warm to room temperature and then is quenched with 3 N HCl until the solution becomes acidic. The product is extracted with dichloromethane, dried over magnesium sulfate, and stripped of solvent to give the corresponding aldehydes in almost pure form. Further purification by distillation furnished pure products which were characterized by their bp, IR, ^{13}C NMR, ^1H NMR, and TLC.

(8) Spectroscopic evidence showed that the alcohol side product was detectable in some cases (≲5%) but could be easily removed in the purification of the crude product.

Acknowledgment. Support of our work by the National Science Foundation is gratefully acknowledged.

Registry No. 1 (R_1 = C_2H_5, R_2 = R_3 = H), 683-08-9; 1 (R_1 = i-C_3H_7, R_2 = R_3 = H), 1445-75-6; 1 (R_1 = C_2H_5, R_2 = CH_3, R_3 = H), 78-38-6; 1 (R_1 = i-C_3H_7, R_2 = CH_3, R_3 = H), 1067-69-2; 1 (R_1 = C_2H_5, R_2 = R_3 = CH_3), 1538-69-8; 1 (R_1 = R_2 = C_2H_5, R_3 = H), 18812-51-6; 2 (R_1 = C_2H_5, R_2 = R_3 = H), 41849-03-0; 2 (R_1 = i-C_3H_7, R_2 = R_3 = H), 91210-94-5; 2 (R_1 = C_2H_5, R_2 = CH_3, R_3 = H)., 91210-95-6; 2 (R_1 = i-C_3H_7, R_2 = CH_3, R_3 = H), 91210-96-7; 2 (R_1 = C_2H_5, R_2 = R_3 = CH_3), 91210-97-8; 2 (R_1 = R_2 = C_2H_5, R_3 = H), 91210-98-9; 3, 4394-85-8; 5 (R_1 = C_2H_5, R_2 = R_3 = H), 1606-75-3; 5 (R_1 = i-C_3H_7, R_2 = R_3 = H), 43186-09-0; 5 (R_1 = C_2H_5, R_2 = CH_3, R_3 = H), 34403-79-7; 5 (R_1 = i-C_3H_7, R_2 = CH_3, R_3 = H), 67398-17-8; 5 (R_1 = C_2H_5, R_2 = R_3 = CH_3), 35078-65-0; 5 (R_1 = R_2 = C_2H_5, R_3 = H), 32329-34-3; $C_6H_5CH_2CH_3MgCl$, 90878-19-6; $C_6H_5CH{=}CHMgBr$, 30094-01-0; $C_6H_5CH_2MgCl$, 6921-34-2; c-C_5H_9MgBr, 33240-34-5; C_6H_5MgBr, 100-58-3; C_6H_5Li, 591-51-5; $C_6H_5C{\equiv}CLi$, 4440-01-1; $C_6H_5CH_2CH_2CHO$, 104-53-0; $C_6H_5CH{=}CHCHO$, 104-55-2; $C_6H_5CH_2CHO$, 122-78-1; c-C_5H_9CHO, 872-53-7; C_6H_5CHO, 100-52-7; $C_6H_5C{\equiv}CCHO$, 2579-22-8; n-butyllithium, 109-72-8; norbornyl-MgBr, 51243-73-3; 1-naphthyl-MgBr, 703-55-9; norbornyl-CHO, 19396-83-9; 1-naphthyl-CHO, 66-77-3; n-butyl-CHO, 110-62-3; lithium, 7439-93-2.

Kinetic and Thermodynamic Control in the Metalation of Pyridine. A Direct Synthesis of 2- and 4-Substituted Pyridines

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We recently[1] succeeded in directly metalating pyridine with the complex of BuLi and t-BuOK[2] in a mixture of tetrahydrofuran (THF) and hexane.

The results of quenching the obtained solution with deuteriomethanol, dimethyl disulfide and trimethylchlorosilane indicated that the metalation had afforded a mixture of approximately equal amounts of 2- and 4-potassio derivatives of pyridine in addition to a minor quantity of the 3-potassio compound (~10 rel %). The ratio 2-: 3-: 4-potassiopyridine was completely different from the ratio of the rates with which the 2-, 3-, and 4-

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(2) Lochman, L.; Pospisil, J.; Lim, D. *Tetrahedron Lett.* **1966**, 127. Schlosser, M. *J. Organomet. Chem.* **1967**, *8*, 9.

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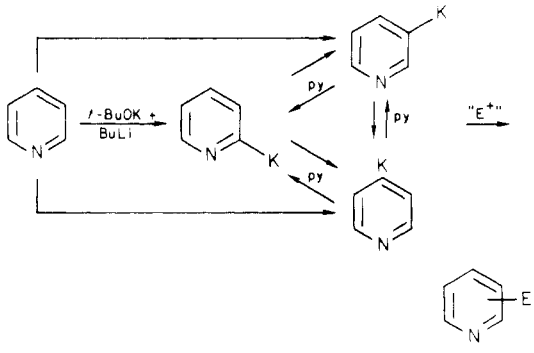
protons in pyridine were exchanged for deuterium upon heating pyridine in CH_3OD at about 160 °C with sodium methoxide.[3] Hoffman et al.[4] calculated a stability order of 3 > 4> 2 for the anions of pyridine. This contrast prompted us to study the metalation of pyridine more closely, and we here report some results that shed light on the matter.

Addition at −100 °C of a 200–300% *excess* of *pyridine* to the complex of BuLi and *t*-BuOK in a mixture of THF and hexane, followed by reaction with various electrophilic reagents, gave mixtures of 2-, 3-, and 4-substituted pyridines. The ratio of the 2, 3, and 4 derivatives appeared to depend strongly upon the length of the time between addition of pyridine to the base and addition of the reagent. There was a gradual shift from 4:1:4 (time interval ~20 min) to about 2:3:15 (120 min). We have not extended this series of experiments with longer intervals, since a ratio comparable with the last one could be attained very soon after addition of hexamethylphosphoric triamide (HMPT). [HMPT was not added until after the pyridine, because HMPT is decomposed by BuLi–*t*-BuOK even at −100 °C.] The final ratio of 0.5:1:10 was reached about 60 min after addition of the HMPT. A totally different ratio of 90:3:7 was obtained when pyridine was *slowly added* to a *100% excess* of *BuLi–t-BuOK* in *diethyl ether*, hexane, and only a very small amount of THF, and the reagents were introduced after about 1.5 h (it was assumed that metalation under these conditions proceeded much more slowly than in a more polar medium). In the third experiment BuLi in hexane was cautiously added at −100 °C to a mixture of pyridine (100% excess) and *t*-BuOK in THF and HMPT. Ten to fifteen minutes after this addition quenching with CH_3SSCH_3 or Me_3SiCl was carried out. This afforded predominantly 4-(methylthio)pyridine (only ~10–12 rel % 2- and 3-isomer present) in about 50% of predominantly 4-(trimethylsilyl)pyridine (10–15 rel % of the other isomers) in 75% yield, respectively.

The results may be explained by assuming the following set of reactions.



E = D, CH_3S, $(CH_3)_3Si$, Se, I

Under weakly polar conditions (diethyl ether) the base has a preference for abstraction of the proton adjacent to nitrogen, because the reaction is assisted by the heteroatom (compare the usual "heteroatom" effect operative during metalation of thiophenes, furans, pyrroles, etc., which directs the metalation to the adjacent position).

In a more polar medium the metalation pattern may be determined by two important counterating effects: (a) the electron-withdrawing resonance and inductive effects of nitrogen favor abstraction of 2-(6) and 4-protons particularly and (b) the repulsion between the free pair on nitrogen and the adjacent negative charge, the latter being more pronounced under polar conditions. These effects do not only operate kinetically (by influencing the ratio of the metalated pyridines in polar medium) but also thermodynamically. Our results of experiments with excess of pyridine and HMPT indicate that in *polar* medium metalation in the 4-position is favored thermodynamically *and* kinetically: the equilibrium situation can be approached by addition of pyridine—which acts as a proton donor—and HMPT, which facilitates the deprotonations by increasing the polarity of the bonds between pyridine and the metal.

The outcome of our experiments with the strong base BuLi-*t*-BuOK in strongly polar medium can best be compared with the data derived by Zoltewicz et al.[3] from their exchange experiments with pyridine-d_5 in polar liquid ammonia as a solvent and $NaNH_2$ as base; their exchange ratio at the 2-, 3-, and 4-position was 0.5:36:240. However, our data are not in agreement with the outcome of extended Hückel calculations.[4] 2-, 3-, and 4-substituted pyridines in general show a considerable difference in volatility. This allows purification by distillation; this is particularly efficient when the mixture consists of one major component as in our case.

Experimental Section[9]

a. Metalation in Weakly Polar Medium. In a 1-L round-bottomed flask (gas-inlet, dropping funnel, stirrer, thermometer + gas outlet) were placed successively 0.20 mol of potassium *tert*-butoxide (Dynamit-Nobel, B.R.D.), 40 mL of dry THF, and 200 mL of dry diethyl ether. The mixture was cooled to −105 °C and a solution of 0.20 mol of BuLi in 140 mL of hexane was cautiously run in, while keeping the temperature close to −100 °C (bath with liquid nitrogen). Pyridine (0.10 mol in 80 mL of diethyl ether, dried over powdered KOH) was subsequently added dropwise in 45 min. During this addition and also 1.5 h after completion of the addition the temperature was maintained at −100 °C. Tetrahydrofuran (50 mL) was then added and the temperature was allowed to rise to −25 °C; the excess of BuLi–*t*-BuOK was destroyed by reaction with THF. The solution was subsequently cooled to −50 °C and a solution of 0.12 mol of lithium bromide in 40 mL of THF was added in 5 min. The mixture was then further cooled to −80 °C, after which reaction with the various reagents was carried out.

Dimethyl disulfide (0.12 mol) or trimethylchlorosilane (0.15 mol) was added in one portion, with vigorous stirring, allowing the temperature to rise.

A solution of iodine (0.15 mol) in 120 mL of diethyl ether was added in one portion at −80 °C, after which the temperature was allowed to rise. In all cases the workup was started with the addition of 150 mL of water (in the case of the iodination reaction an aqueous solution of 10 g of $Na_2S_2O_3$ was added). The aqueous layer was extracted 3 times with diethyl ether. The combined organic solutions were dried over K_2CO_3. After removal of the solvents in vacuo the remaining liquids were distilled (the products from a number of experiments were collected) through an efficient column to give 2-substituted pyridines in 60–65% yields. The purity as determined by GLC and ^1H and ^{13}C NMR spectroscopy was at least 95%, the main contaminants being the other isomers. Our physical properties (bp, n_D) corresponded satisfactorily with literature data.[5-8]

For ^{13}C NMR spectra, see Table I.

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(8) King, H.; Ware, L. L. *J. Chem. Soc.* **1939**, 875.
(9) All reactions were carried out under nitrogen.

Table I. ^{13}C NMR Spectral Data of 2- and 4-Substituted Pyridines[a]

substituent	δ values C2 C6	C3 C5	C4	subst
2-SCH_3	159.0	118.1	134.8	12.2
	148.5	120.5		
4-SCH_3	148.6	119.3	149.6	13.1
	148.6	119.3		
2-I	117.7	134.3	137.0	
	150.0	122.4		
4-I	150.0	132.8	105.1	
	150.0	132.8		
2-$SiMe_3$	167.8	128.1	133.3	-2.3
	150.0	122.1		
4-$SiMe_3$	147.9	127.2	149.1	-2.6
	147.9	127.2		
4-$SeCH_3$	148.5	122.6	144.0	4.7
	148.5	122.6		

[a] Concentrations about 25% (v/v), solvent $CDCl_3$.

b. Metalation in Strongly Polar Medium. In the reaction flask (see a) was placed a solution of 0.11 mol of *t*-BuOK in 80 mL of THF, 0.20 mol of pyridine, and 40 mL of HMPT (dried by adding a sufficient quantity of a concentrated solution of lithium—3 g/100 mL—in liquid ammonia until the blue color persisted and subsequently distilling twice at 10–15 mmHg). The mixture was cooled to −105 to −110 °C and a solution of 0.10 mol of butyllithium in 70 mL of hexane was added in 10 min, with efficient stirring and cooling between −100 and −110 °C.

After the addition, the light-yellow solution was stirred for an additional 15 min at −100 °C; then Me_3SiCl (0.15 mol) or CH_3SSCH_3 (0.14 mol) was added in one portion. In the case of iodination and reaction with selenium first a solution of 0.12 mol of anhydrous lithium bromide was added at −100 °C and after 5 min a solution of 0.15 mol of iodine in 100 mL of THF was poured to the reaction mixture or 0.10 mol of powdered red selenium was introduced. After the addition of the reagents the temperature was allowed to rise to −10 °C. In the case of selenation 0.15 mol of methyl iodide was then added. The reaction mixtures were subsequently diluted with 200 mL of water or aqueous solution of 10 g of $Na_2S_2O_3$.

The aqueous layer was extracted 5–8 times with small portions of diethyl ether. The combined solutions were dried over K_2CO_3 and the concentrated in vacuo. In order to remove the HMPT present in the remaining liquid, water (100 mL) was added and ten extractions with 2:1 mixture of pentane and diethyl ether were carried out. Each extract was washed twice with 30-mL portions of water, the aqueous layers being added to the main aqueous layer. The combined extract were dried over K_2CO_3 and then concentrated in vacuo. Careful distillation of the remaining liquids afforded the reasonable pure 4-substituted pyridine in yields of 50–55% (the actual yields are about 20% higher, but the fractionated distillations gave rise to some losses).

4-Methylthiopyridine and 4-iodopyridine, were obtained in a pure state by crystallization at −20 °C from a 3:1 mixture of pentane and diethyl ether. Our 2-(methylseleno)pyridine has bp 100 °C/20 min, n_D^{20} min, n_D^{20} 1.6147. For physical constants of the pyridine derivatives, see ref 6–8; for ^{13}C NMR spectral data, see Table I.

c. Isolation of the Deuterated Pyridines. After the metalation (a) had been completed, the cold (−100 °C) reaction mixture was poured in 2–3 min into a vigorously stirred solution of 0.4 mol of deuteriomethanol in 100 mL of diethyl ether, with cooling below −20 °C (applying inverseorder addition gave appreciable amounts of dideuterated and nondeuterated pyridine).

After this quenching procedure a mixture of 40 mL of 36% hydrochloric acid and 60 mL of water was added. The layers were separated and the organic layer washed 1 time with 50 mL of water. The combined aqueous layers were freed from organic solvents by heating them in vacuo (rotary evaporator). Subsequently potassium hydroxide pellets (100 g) were added with shaking and cooling in ice–water. The deuterated pyridine liberated was isolated by extraction (5 times) with diethyl ether, drying the extracts over powdered KOH, and subsequently distilling at normal pressure. The yield of deuterated pyridine (~90% 2-isomer) was about 95%.

Registry No. CH_3SSCH_3, 624-92-0; Me_3SiCl, 75-77-4; pyridine, 110-86-1; 2-potassiopyridine, 91238-49-2; 3-potassiopyridine, 91238-50-5; 4-potassiopyridine, 91238-51-6; iodine, 7553-56-2; selenium, 7782-49-2; deuteriomethanol, 1455-13-6; 2-(methylseleno)pyridine, 88871-79-8; 2-(methylthio)pyridine, 18438-38-5; 4-(methylthio)pyridine, 22581-72-2; 2-iodopyridine, 5029-67-4; 4-iodopyridine, 15854-87-2; 2-(trimethylsilyl)pyridine, 13737-04-7; 4-(trimethylsilyl)pyridine, 18301-46-7; 4-(methylseleno)pyridine, 91238-52-7; pyridine-2-d_1, 1807-97-2.

(10) When this work was finished a paper of Martin et al. (*J. Org. Chem.* **1983**, *48*, 4158) dealing with the ortho-metalation of pyridines with lithium tetramethylpiperidide came to our attention.

A Convenient Synthetic Route to (*E*)-2-Penten-1-ol

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(*E*)-2-Penten-1-ol (**1**) is of interest as a common precursor for the synthesis of the achiral aliphatic components of some insect sex pheromones which have a terminal unsaturated five-C atom unit of *E* configuration.[1] In connection with our work on this synthetic area, we required comparatively large amounts of **1**.

The few procedures reported in the literature for its preparation involve allylic rearrangements[2] or stereospecific hydrogenation of 2-pentyn-1-ol.[3] The former procedures give a mixture of geometrical isomers, while the latter is not suitable for large-scale preparations. Consequently, efforts were focused on the development of a convenient and economically feasible route for preparing **1**.

Our approach was based upon the selective reduction of (*E*)-2-pentenoic acid(**2**) and/or its derivatives which, to the best of our knowledge, has not been reported. **2** was obtained in good yield by Knoevenagel–Doebner condensation between propionaldehyde and malonic acid. Stereocontrol of the reaction was achieved at 20 °C in absence of light, and the thermodynamically more stable *E* isomer was formed almost quantitatively. It should be noted that in the case of α,β-unsaturated acids and esters the β-carboxylic or β-carbalkoxy group, respectively, has a deshielding effect on the *cis*-vinylic proton. The differential shielding of the *cis*- and *trans*-vinylic protons allows calculation of the cis/trans isomer distribution.[4]

Initial attempts at reducing **2**, (*E*)-2-pentenoic acid chloride (**2a**), and methyl (*E*)-2-pentenoate (**2b**) by pro-

(1) For a comprehensive review, see: Rossi, R. *Synthesis* **1977**, 817.
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