metric measurements were not possible because the current efficiency was less than 100%. The electrolysis was continued until the current dropped almost to zero. The disappearance of ketone was also followed by CV. On completion of the electrolysis, the catholyte was diluted with a very large excess of distilled water (800–1000 ml) and extracted several times with a total of 500 ml of ether. The combined ether extract was washed with several portions of distilled water, saturated sodium bicarbonate solution, again with portions of distilled water, and finally with two portions of saturated sodium chloride solution. The extract was dried overnight over anhydrous magnesium sulfate. After filtration, the ether was removed by evaporation under reduced pressure until the crude product reached a constant weight. At this point the crude product weighed 10.5 g.

An aliquot of the crude product (1.05 g) was column chromatographed on 60 g of silica gel using hexane–benzene mixtures for elution. The material (0.89 g, 66%) eluting with 3:1 hexane–benzene showed a single spot on thin-layer chromatography and was the pure ketoacetate **5**: viscous oil; nmr (CCl_4, internal TMS) δ 1.95 (s, 3), 2.02 (s, 3), 7.2 ppm (m, 10); ir (10% in CCl_4) 3030 (m), 1750 (s), 1725 (s), 1490 (m), 1450 (m), 1430 (sh), 1370 (m), 1350 (sh), 1235 (s), 1180 (sh), 1160 (m), 1080 (w), 1020 (m), 950 (m), 920 (w), 890 (m), 695 cm^{-1} (s). An analytical sample was prepared by rechromatography over silica gel. *Anal.* Calcd for $C_{17}H_{16}O_3$: C, 76.10; H, 6.01. Found: C, 75.85; H, 6.22.

$LiAlH_4$ Reduction of Ketoacetate 5. To a suspension of $LiAlH_4$ (1.5 mmol) in anhydrous ether (5 ml), a solution of the ketoacetate **5** (300 mg, 1.1 mmol) in anhydrous ether (5 ml) was added dropwise with continuous stirring. After stirring for 1 hr at room temperature, excess $LiAlH_4$ was destroyed by dropwise addition of ethyl acetate, followed by 100 ml of 10% ammonium chloride solution. The mixture was then extracted with ether, the ether extract washed with portions of distilled water and saturated sodium chloride solution, and the extract dried overnight over anhydrous magnesium sulfate. Removal of the ether by vacuum evaporation left an oily liquid (220 mg) which solidified on standing. The crude solid had a mp of 90–92°. It was purified by recrystallization from hexane: mp 95–96°; nmr ($CDCl_3$, internal TMS) δ 1.05 (d, 3, CH_3CH), 2.00 (d, 1, CHOH), 3.12 (s, 1, COH), 4.75 (m, CH–O), 7.3 ppm (m, 10, ArH); ir (10% in CCl_4) 3550 (m), 3000 (b), 1595 (w), 1490 (m), 1450 (m), 1387 (m), 1350 (m), 1320 (w), 1260 (m), 1170 (m), 1130 (w), 1100 (m), 962 (m), 920 (w), 892 (m), 877 (m), 700 (s), 654 (m), 635 cm^{-1} (m).

Synthesis of 1,1-Diphenyl-1,2-propanediol.[22] In a three-necked 500-ml flask fitted with a separatory funnel, reflux condenser, and mechanical stirrer was prepared in the conventional manner a Grignard reagent from 27 g of magnesium turnings and 181 g of bromobenzene in 450 ml of ether. The reagent was cooled in an ice bath while freshly distilled ethyl lactate (29 ml) was added slowly. The excess Grignard reagent was decomposed by the addition of 150 ml of ammonium chloride solution (50 g in 150 ml). The ether layer was separated and washed with portions of distilled water and saturated sodium chloride solution. After drying over anhydrous magnesium sulfate, the ether was removed by vacuum evaporation. The crude white solid (mp 88–90°) was recrystallized several times from hexane to a constant melting point of 95–96°. The infrared and nmr spectra of this product were identical with that of the diol obtained by $LiAlH_4$ reduction of ketoacetate **5**. A mixture melting point of the two products was not depressed.

Registry No.—**5**, 13294-67-2; **7**, 52183-00-3; benzaphenone, 119-61-9.

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Selective Acylation of 2,4-Lutidine at Its 2- and 4-Methyl Groups

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2,4-Lutidine (**1**) has been acylated preferentially at its 2- or 4-methyl group depending on the condensing agent. It is suggested that if the metallic portion of the condensing agent can coordinate with the nitrogen atom of **1**, then the 2-methyl group of **1** is acylated; otherwise, the 4-methyl group is acylated. The acylation of **1** at its 2-methyl group has also been effected in high yields with three perfluorinated esters using phenyllithium as the condensing agent.

2,4-Lutidine (**1**) reacts selectively[1] with alkyl halides, aldehydes, and ketones at its 2- or 4-methyl group depending on the condensing agent.

We now report the selective lateral acylation of the 2- and 4-methyl groups of **1**. Earlier it was shown that 2-picoline[2] and 4-picoline[3] can be laterally metalated, the former by organolithium reagents and the latter by sodium amide in liquid ammonia.

Only one acylation of **1** could be found in the literature; its benzoylation using phenyllithium as the condensing agent[4,5] gave exclusively 4-methyl-2-phenacylpyridine in good yield. These results agree with a later study by Teague, *et al.*,[6] who showed that the reaction of **1** with benzaldehyde using phenyllithium gave exclusively 1-phenyl-2-(4-methyl-2-pyridyl)ethanol.

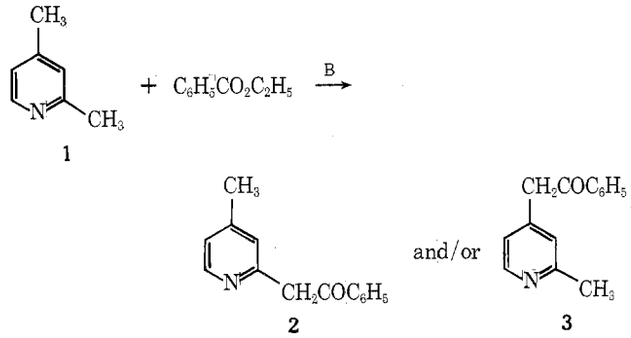
In the present study, **1** was acylated with ethyl benzoate

Table I
Monobenzoylation of 2,4-Lutidine with Ethyl Benzoate[a]

Condensing agent	% 2,4-lutidine recovered	% yield of 4-methyl-2-phenacylpyridine	% yield of 2-methyl-4-phenacylpyridine	% yield of azomethine addition product
n-Butyllithium	44	67[b,c]	3[b,d]	11[e]
Phenyllithium	50	72[b,c]	0	5[f]
Sodium amide	49	0	85[b,d]	0
Phenylsodium	53	60[b,c]	12[b,d]	*g*

[a] Molar ratio of tar base–condensing agent–ester is 2:2:1 in all the reactions. [b] Yield based on ester. [c] Mp 57.0–58 2° (from ethanol–water). *Anal.* Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6 20; N, 6.63. Found: C, 79.51; H, 6.12; N, 6.55. For the literature value [bp 159–160° (1.8 mm)], see ref 4. Picrate, mp 155.5–156.5° [lit. value 167–168° (see ref 4) and 153° (see ref 5)]. *Anal.* Calcd for $C_{20}H_{16}N_4O_8$: C, 54.54; H, 3.66; N, 12.72. Found: C, 54.69; H, 3.80; N, 12.77. [d] Bp 136–144° (0.25 mm), mp 80.8–81.8° (from aqueous ethanol). *Anal.* Calcd for $C_{14}H_{13}NO$: C, 79.59; H, 6.20; N, 6.63. Found: C, 79.41; H, 6.16; N, 6.58. Picrate, mp 144.0–145.5°. *Anal.* Calcd for $C_{20}H_{16}N_4O_8$: N, 12.72. Found: N, 12.60. [e] Infrared spectrum showed a relatively strong aliphatic C–H stretching band at 3.40 μ and an absorption band at 11.85 μ, characteristic of a 2,4,6-trialkylpyridine (see ref 17); the nmr spectrum is in good agreement with 2-*n*-butyl-4,6-dimethylpyridine. [f] Infrared (absorption peaks at 11.8 and 12.9 μ) and nmr spectra are in good agreement with 2,4-dimethyl-6-phenylpyridine. [g] Not determined.

in good to high yields using four different condensing agents (Table I). In all the reactions a 2:2:1 molar ratio of the tar base–condensing agent–ester was used.[7] Theoretically, two isomeric ketones, **2** and **3**, can be formed.



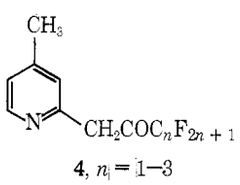
The benzoylation of **1** using *n*-butyllithium and phenyllithium gave **2** almost exclusively whose structure was assigned from its nmr spectrum. In addition small amounts of the azomethine addition products, 2-*n*-butyl-4,6-dimethylpyridine (11%) and 2-phenyl-4,6-dimethylpyridine (5%), were formed. By contrast, sodium amide in liquid ammonia gave only **3** (85%), whose structure was supported by its nmr spectrum. In addition, employing phenylsodium in benzene there was obtained **2** (60%) and **3** (12%). We agree with the suggestion made by Kaiser, *et al.*,[1] that *n*-butyllithium and phenyllithium metalate **1** essentially only at the 2-methyl group *via* the coordination of the lithium cation on the ring nitrogen atom.

In the benzoylation of **1** using phenylsodium in benzene as the condensing agent, the preference for metalation at the 2-methyl group is considerably less than with phenyllithium in ether. This result can be rationalized. The carbon–sodium[8] bond in phenylsodium (A) is more ionic than the carbon–lithium[8] bond in phenyllithium (B). Thus, A acts as a stronger base than B and removes a proton from both the 2- and 4-methyl groups of **1** to give the corresponding monosodium derivatives. The fact that a proton on the 2-methyl group is removed more extensively than a proton on the 4-methyl group suggests that A, although it probably does so to a smaller degree than B, complexes with the ring, nitrogen atom. This would enable the anionic portion of the phenylsodium to remove a proton more effectively from the 2- than from the 4-methyl group of **1**.

In contrast with these results the use of sodium amide in anhydrous liquid ammonia gave essentially exclusive metalation of the 4-methyl group of **1**. Kaiser, *et al.*,[1] have observed that **1** is alkylated at the 4-methyl group using similar reaction conditions. These workers[1] suggest two explanations for their results: (1) the sodium cation is not as effective as the lithium cation in coordinating with the nitrogen atom of **1** and (2) the sodium cation of sodium amide is complexed with ammonia molecules with the result that the amide ion is more available for ionizing the more acid hydrogen atoms of the 4-methyl group. We propose an alternate explanation, *viz.*, a steric effect may be involved *via* hydrogen bond formation between the nitrogen atom of **1** and the liquid ammonia solvent.[9] The presence of a bulky group attached to the nitrogen atom of **1**, as represented by ammoniated **1**, could offer steric hindrance to the approach of the sodium amide to the 2-methyl group and thus reduce the tendency for metalation at this group.

2,4-Lutidine (**1**) was also acylated with ethyl propionate using sodium amide in liquid ammonia as the condensing agent to give 2-methyl-4-(propionylmethyl)pyridine (45%) and the carbinol, 2-ethyl-1,3-bis(2-methyl-4-pyridyl)propanol-2.

In addition (Table II), **1** was acylated with three perfluoroalkyl esters using phenyllithium. Results comparable to the benzoylation of **1** were obtained to give ketones of type **4**. Higher yields of ketones were obtained using the reverse



4, $n_i = 1–3$

addition technique, *i.e.*, 2-lithiomethyl-4-methylpyridine was added to the esters, than when the esters were added to the tar base anion.

Although **1** can be metalated at the 4 position by sodium amide when the reaction is effected in liquid ammonia, *vide supra*, this system cannot be used to effect its acyla-

Table II
Ketones of the Type 4-$CH_3C_5H_3CH_2COR$-2

Ester	R	Yield, %	Mp, °C	Formula	Anal., % Calcd C	Calcd H	Found C	Found H
$CF_3CO_2C_2H_5$	CF_3	72.6,[a] 91.2[b]	130.5–131.2[c]	$C_9H_8F_3NO$[d]	53.20	3.94	53.07	4.17
$C_2F_5CO_2C_2H_5$	C_2F_5	42.5,[a] 83.8[b]	135.6–138[c]	$C_{10}H_8F_5NO$[e]	47.43	3.16	47.43	3.14
n-$C_3F_7CO_2C_2H_5$	n-C_3F_7	45.0,[a] 60.0[b]	110.5–111.6[c]	$C_{11}H_8F_7NO$[f]	43.56	2.64	43.32	2.77

[a] SA, standard addition. [b] RA, reverse addition. [c] From Skelly B. [d] Olive green copper salt, mp 230–232°. [e] Brown copper salt, mp 211.5–214.0°. [f] Tan copper salt, mp 185.0–186.0°.

tion with perfluoroalkyl esters since they are rapidly ammonolyzed.[10,11]

To avoid the use of liquid ammonia in preparing 2-methyl-4-picolyl perfluoroalkyl ketones attempts were made to prepare the 2-methyl-4-picolyl anion in the absence of liquid ammonia. The ammonia in a mixture of sodium amide and liquid ammonia was replaced by THF and 1 was then added. After a 6.5-hr reflux period ethyl trifluoroacetate was added to a solution to give a small amount (<1 g) of the 2-acylated product, 4-methyl-2-trifluoroacetyl methylpyridine. Extending the anion formation time to 44 hr resulted in the formation of this product in only an 11% yield.

These results indicate that anion formation involving 1 occurs at the 2-methyl group with sodium amide in THF, whereas metalation by sodium amide in liquid ammonia occurs at the 4-methyl group. Sodium amide in the somewhat polar solvent THF probably metalates the 2-methyl group of 1 for a reason comparable, *vide supra,* to the metalation of this methyl group by phenyllithium in ether and *n*-butyllithium in hexane.

It was desirable to attempt the acylation of 1 in a solvent which can solvate cations. By preferentially complexing with the potentially available sodium ion of sodium amide such a solvent would inhibit complexing between the sodium cation with the pyridyl nitrogen atom and would allow the amide ion to remove a proton from the more reactive 4-methyl group.[12,13]

Because dimethyl sulfoxide (DMSO) has been reported[14] to strongly solvate cations, it was the logical choice. To test the feasibility of this reaction, the acylation of 1 with ethyl benzoate was attempted using the DMSO anion, the strongest base which can exist in a DMSO solution,[15] as the condensing agent. The desired 4-acylated compound, 2-methyl-4-phenacylpyridine, was obtained in low yield (19%). Unfortunately, the reaction could not be extended to include the acylation of the 4-methyl group of 1 by perfluorinated esters since several attempts gave only polymeric materials.

Infrared and nmr spectroscopy were used to confirm the structure of 4-methyl-2-phenacylpyridine. Our results agree with those of Branch, *et al.*,[16] who have shown that this and related ketones do not exist in the keto form but rather in a conjugated chelated form. By contrast, the infrared spectrum of the solid ketone, 2-methyl-4-phenacylpyridine, showed a strong C=O absorption band at 5.95μ microns and no evidence of conjugate chelation.

Experimental Section

(1) General Procedure for Acylation Reactions. Acylation of 2,4-Lutidine Using Lithium Bases. All monoacylations of 2,4-lutidine were carried out using the procedure of Levine, *et al.*,[2] for the acylation of 2-picoline with esters using phenyllithium as the condensing agent.

(2) Acylation of 2,4-Lutidine and Its Derivatives. Acylation of 2,4-Lutidine with Esters Using Various Condensing Agents. (a) Using a 2:2:1 Molar Ratio of 2,4-Lutidine:*n*-Butyllithium:Ethyl Benzoate. To *n*-butyllithium (0.4 mol as a 1.61 *M* solution in *n*-hexane) in 400 ml of anhydrous ether was added 2,4-lutidine (0.4 mol, 42.8 g) over a 20-min period. The solution was stirred for 30 min at room temperature. Ethyl benzoate (0.2 mol, 30.0 g), dissolved in an equal volume of anhydrous ether, was added (25 min). The solution was stirred for 45 min at room temperature and processed in the customary manner. Distillation of the crude product mixture gave (a) 23.7 g of light yellow liquid, bp 75–128° (50 mm), and (b) 31.3 g of 4-methyl-2-phenacylpyridine, bp 154–160° (1.3 mm). Fraction a was analyzed by gas chromatography and was shown to consist of two compounds: (1) 2,4-lutidine (79%) and (2) 2-*n*-butyl-4,6-dimethylpyridine (21%). The ir spectra of the ketone in both liquid and solid forms are in good agreement with the assigned structure, 4-methyl-2-phenacylpyridine.[16] Although the nmr spectrum of the ketone taken prior to recrystallization agrees essentially with the proposed structure, 4-methyl-2-phenacylpyridine, three minor extraneous peaks are present at 6.02, 7.62, and 9.05 ppm. The peak at 9.05 ppm indicates the possible presence of an *n*-alkyl group possibly attributable to the *n*-butyl group in 2-*n*-butyl-4,6-dimethylpyridine. The two peaks at 6.02 and 7.62 ppm suggest the presence of the methylene group and the 2-methyl group, respectively, of 2-methyl-4-phenacylpyridine. It was calculated that the maximum concentrations of 2-*n*-butyl-4,6-dimethylpyridine and 2-methyl-4-phenacylpyridine present in the ketone, fraction b, are 6.4 and 3.6%, respectively. These results show that the minimum ratio of acylation at the 2 position to acylation at the 4 position of 2,4-lutidine is 25:1. Thus, there were obtained 18.7 g (44% recovery) of 2,4-lutidine, 7.0 g (10.7%) of 2-*n*-butyl-4,6-dimethylpyridine, 1.1 g (2.6%) of 2-methyl-4-phenacylpyridine, and 28.2 g (67%) of 4-methyl-2-phenacylpyridine.

(b) Using a 2:2:1 Molar Ratio of 2,4-Lutidine:Phenyllithium:Ethyl Benzoate. The interaction of phenyllithium (0.4 mol, prepared from 0.8 g-atom (5.55 g) of lithium metal and 0.4 mol (62.8 g) of bromobenzene), 2,4-lutidine (0.4 mol, 42.8 g), and ethyl benzoate (0.2 mol, 30.0 g) gave (a) 21.3 g (50% recovery) of 2,4-lutidine, bp 76–80° (50 mm), (b) 3.4 g of yellow liquid, bp 118–148° (1.0 mm), and (c) 32.7 g of crude 4-methyl-2-phenacylpyridine, bp 125–145° (0.2 mm). There were obtained 21.3 g (50% recovery) of 2,4-lutidine, 3.4 g of a mixture of 2,4-dimethyl-6-phenylpyridine and 4-methyl-2-phenacylpyridine, and 32.7 g of a mixture containing 2.3 g (3.1%) of 2,4-dimethyl-6-phenylpyridine and 30.4 g (72%) of 4-methyl-2-phenacylpyridine.

(c) Using a 2:2:1 Molar Ratio of 2,4-Lutidine:Sodium Amide:Ethyl Benzoate. To 0.4 mol of sodium amide in 500 ml of anhydrous liquid ammonia was added a solution of 2,4-lutidine (0.4 mol, 42.8 g) in 50 ml of anhydrous ether over a 20-min period. A solution of ethyl benzoate (0.2 mol, 30.0 g) in 30 ml of ether was added and the mixture was stirred for 1 hr. Ammonium chloride, 25 g, was added slowly and the ammonia was removed and replaced by ether. The reaction mixture was processed by the normal procedure. Distillation gave 21.0 g (49%) of recovered 2,4-lutidine, bp 75–77° (55 mm), 36.0 g (85%) of 2-methyl-4-phenacylpyridine, bp 136–144° (0.25 mm), and 1.7 g of a tarry distillation residue. The yellow viscous, liquid ketone solidified shortly after collection, mp 80.8–81.8° from aqueous ethanol; monopicrate, mp 144.0–145.5°. The ir of the solid ketone as a Nujol mull shows a strong carbonyl band at 5.9 μ.

(d) Using a 2:2:1 Molar Ratio of 2,4-Lutidine:Phenylsodium:Ethyl Benzoate. Phenylsodium was prepared from sodium (15.9 g, 0.69 g-atom) and bromobenzene (47.1 g, 0.3 mol) in 200 ml of anhydrous toluene as described earlier.[17] To the dark brown mixture was added a solution of ethyl benzoate (0.15 mol, 22.5 g) in 25 ml of dry benzene; stirring was continued for 30 min at 10–15°. The reaction was processed by the usual procedure. Distillation gave 17.0 g (55% recovery) of 2,4-lutidine, bp 75–77° (50 mm), 22.9 g (72%) of a mixture of 4-methyl-2-phenacylpyridine and 2-methyl-4-phenacylpyridine, bp 150–157° (1.0 mm), and 2.5 g of a tarry distillation residue. The ir of the ketone mixture agrees with that of 4-methyl-2-phenacylpyridine although a small amount of 2-methyl-4-phenacylpyridine was present by comparison with the spectrum of the latter compound. The methyl protons of the 2- and 4-methyl groups on a pyridine ring have τ values of 7.64 and 7.93 ppm in the nmr spectrum. Quantitative nmr analysis showed that the ketone mixture contains 4-methyl-2-phenacylpyridine (83%) and 2-methyl-4-phenacylpyridine (17%). This corresponds to yields of 60 and 12%, respectively.

(e) Using a 2:2:1 Molar Ratio of 2,4-Lutidine:Sodium Amide:Ethyl Propionate. To 0.4 mol of sodium amide in 500 ml of anhydrous liquid ammonia was added a solution of 2,4-lutidine (0.4 mol, 42.8 g) in 50 ml of anhydrous ether. The mixture was stirred for 2 hr, followed by the addition of ethyl propionate (0.2 mol, 20.4 g) in 20 ml of ether. It was stirred for 1.25 hr and neutralized with 25 g of solid ammonium chloride, and the ammonia was replaced by ether. The reaction mixture was processed by the usual procedure. Distillation gave (a) 20.0 g (47% recovery) of 2,4-lutidine, bp 75–77° (50 mm), (b) 14.7 g (45%) of 2-methyl-4-(propionylmethyl)pyridine, bp 143–146° (14.2 mm), and (c) 11.5 g (21%) of 2-ethyl-1,3-bis(2-methyl-4-pyridyl)propanol-2, bp 175–180° (0.3 mm).

Distillate fraction a was identified as 2,4-lutidine (ir). The ir spectrum of distillate fraction b is in agreement with the assigned structure, 2-methyl-4-(propionylmethyl)pyridine (carbonyl absorption band at 5.80 μ and the absorption band at 12.35 μ, charac-

teristic of a 2,4-disubstituted pyridine derivative). The nmr spectrum of fraction b is in good agreement with the proposed structure. The absence of a significant proton resonance peak with a τ value in the range of 7.80–7.95 ppm, arising from the 4-methyl group on the pyridine ring, is evidence for essentially complete acylation at the 4 position. Fraction b was analyzed.

Anal. Calcd for $C_{10}H_{13}NO$: N, 8.58. Found: N, 8.85.

A sample of the ketone was converted to a yellow monopicrate, mp 122.8–124.2°.

Anal. Calcd for $C_{16}H_{16}N_4O_8$: N, 14.28. Found: N, 14.21.

The ir spectrum of the carbinol, fraction c, shows a very strong absorption band at 3.0 μ, characteristic of an O–H group. The nmr spectrum of this product is in good agreement with the assigned structure. The absence of a proton resonance peak at 7.80–7.95 ppm, attributable to the 4-methyl group on the pyridine ring, offers further support for essentially exclusive attack of the sodium amide at the 4-methyl group of 2,4-lutidine. The carbinol was analyzed.

Anal. Calcd for $C_{17}H_{22}N_2O$: C, 75.52; H, 8.20; N, 1036. Found: C, 75.68; H, 8.07; N, 10.18.

(3) Acylation of 2,4-Lutidine with Perfluorinated Esters. (a) Standard Addition Technique. This is the same as the general procedure used above for the other acylation reactions.

(b) Reverse Addition Technique. The acylation of the anion of 1 with an ester employing the reverse addition technique differs from the standard addition procedure in that the 2 equiv of the tar base anion is prepared from phenyllithium and 1 in a reaction vessel which is positioned above and connected to a second reaction vessel. In the bottom flask (three necked), which is equipped with a reflux condenser and a mechanical stirrer, is placed 1 equiv of the appropriate ester and 100 ml of anhydrous ether for every 0.1 mol of ester. The flask containing the ester is cooled to −5° with a salt and ice bath and the solution of the tar base anion is added dropwise. After addition of the anion the reaction mixture is allowed to warm to room temperature, stirred for 1 hr, and processed as with reactions employing the standard addition technique.

(4) The Acylation of 2,4-Lutidine at the 2-Methyl Group with Ethyl Trifluoroacetate Using the Reverse Addition Technique. Using phenyllithium (0.2 mol), 1 (21.4 g, 0.2 mol), and ethyl trifluoroacetate (14.2 g, 0.1 mol) there was obtained 8.48 g (39.6%) of 2,4-lutidine (bp 75° (42 mm)) by distillation. Upon extraction of the distillation residue with Skelly B there was obtained 18.5 g (91.2%) of 4-methyl-2-picolyl trifluoromethyl ketone (mp 130.4–131.8°) and 4.16 g of an intractable residue.

Registry No.—**1**, 108-47-4; **2**, 3197-57-7; **2** picrate, 3197-62-4; **3**, 51975-33-8; **3** picrate, 52920-03-3; **4** (n = 1), 52920-04-4; **4** (n = 1) copper salt, 52920-05-5; **4** (n = 2), 52920-06-6; **4** (n = 2) copper salt, 52920-07-7; **4** (n = 3), 52920-08-8; **4** (n = 3) copper salt, 52920-09-9; n-butyllithium, 109-72-8; phenyllithium, 591-51-5; sodium amide, 7782-92-5; phenylsodium, 1623-99-0; ethyl benzoate, 93-89-0; 2,4-dimethyl-6-phenylpyridine, 27068-65-1; ethyl propionate, 105-37-3; 2-methyl-4-(propionylmethyl)pyridine, 52920-10-2; 2-methyl-4-(propionylmethyl)pyridine picrate, 52920-11-3; 2-ethyl-1,3-bis(2-methyl-4-pyridyl)propanol-2, 52920-12-4; ethyl trifluoroacetate, 383-63-1; ethyl pentafluoropropionate, 426-65-3; ethyl heptafluorobutyrate, 356-27-4; 2-n-butyl-4,6-dimethylpyridine, 52919-93-4.

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Studies on the Coupling Step in Solid Phase Peptide Synthesis. Further Competition Experiments and Attempts to Assess Formation of Ion Pairs[1]

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Competition experiments have been performed to study the possible influence of a number of α-amino protecting groups with urethane structure on the reactivity of amino acids in the coupling step under solid phase peptide synthesis conditions. No differences in reactivity could be detected, however, by this procedure, which we recently used for a similar study on the influence of amino acid side chains. A few additional experiments have been made with peptides instead of amino acids to gain insight into the prospects of fragment coupling. The data to be presented in the first half of this paper have been obtained by amino acid analysis of hydrolyzed peptide mixtures. Insolubilized hydrogen-bonded ion pairs are postulated to be formed on addition of an amino acid derivative in dichloromethane prior to the coupling in solid phase peptide synthesis. In the second half of this paper attempts have been made to determine the extent to which ion pairs are formed under different conditions. The influence of temperature, the concentration of soluble carboxyl component, and the nature of the solvent have been studied.

Peptide synthesis on a solid support, generally called solid phase peptide synthesis (SPPS), was introduced and pioneered by Merrifield[2,3] and is today a well-established technique which has been used for the preparation of many peptides. In this procedure synthesis takes place in a stepwise fashion starting from the carboxyl end, with the growing peptide attached by an ester bond to a polystyrene resin. Since the α-amino function must be protected, one cycle involves exposing the amino group and coupling to it the next amino acid. After a certain number of such cycles the peptide is stripped off the resin. Generally all protecting groups still remaining on the peptide are removed at the same time, leaving a crude free peptide which now has to be purified.