A detailed representative kinetic run is given in Table II.[24] First-order rate plots of log $[CCN]_t/[CCN]_0$ against t yielded straight lines in all cases studied (Figure 5).[24] The second-order rate constants were determined by dividing the pseudo-first-order rate constants by base concentration.

It may be argued that the trans olefin does indeed isomerize to the cis olefin, but that the very minor accumulation of the cis isomer is due to its faster consumption in the addition reaction, as compared to that of the trans olefin. This, however, is not the case as is evident from the fact that the second-order rate constants for the nucleophilic attack step of the ethoxide anion on the *cis*- and on the *trans*-cinnamonitrile are about the same: $k_4 \approx 3.50 \times 10^{-4}$ l. mol^{-1} s^{-1} and $k_1 = (3.72 \pm 0.51) \times 10^{-4}$ l. mol^{-1} s^{-1}.

Experimental Section

The infrared spectra were obtained with a Perkin-Elmer Model 257 spectrophotometer. NMR spectra were recorded on a JEOL 60 MHz spectrometer. VPC measurements were done on a Varian Aerograph Model 1800 gas chromatograph. Mass spectra were recorded on a Hitachi Perkin-Elmer Model RMV-6 (70 eV) mass spectrometer.

Materials. A mixture of *cis*- and *trans*-cinnamonitrile was synthesized[22] and separated by distillation on a spinning band column. The cis and trans isomers were each obtained at 98% purity (VPC). Absolute dry ethyl [^{2}H]alcohol (Miles-Yeda), 99.9% isotopically pure, was used. Ethanolic sodium ethoxide solutions were prepared by adding sodium metal to ethyl [^{2}H]alcohol under reflux and nitrogen. The base concentration was determined by titration with hydrochloric acid. Liquid materials and solutions were kept under pure nitrogen in flasks fitted with self-sealing rubber caps. Aliquot portions were removed from these flasks with syringes by applying nitrogen pressure.

Kinetic Runs. The reactions of *trans*-cinnamonitrile with ethyl [^{2}H]alcohol catalyzed by sodium ethoxide were carried out in a 150-ml flask connected to high vacuum and nitrogen lines. The flask was fitted with a self-sealing rubber cap through which liquids were introduced by syringes. The system was dried, evacuated, and flushed with dry nitrogen prior to the introduction of solvent and reactants. The required amounts of cinnamonitrile and ethyl [^{2}H]alcohol were introduced into the flask which was then immersed in a constant-temperature bath at (39 ± 0.5) °C. A solution of sodium ethoxide in ethyl [^{2}H]alcohol was then introduced and time recorded. Portions of the homogeneous mixture were withdrawn at measured intervals through a capillary stopcock, by applying a nitrogen pressure. The samples withdrawn were quenched with excess acetic acid and subjected to quantitative VPC and ir measurements. Some representative results of kinetic rate measurements of the addition reaction are presented in Table II.[24] The kinetic rate measurements of the addition of ethyl [^{2}H]alcohol to *cis*-cinnamonitrile and its simultaneous isomerization to the trans isomer were followed by VPC.

Quantitative Ir Analysis. The baseline density method[23] was used to determine the percentage of deuterium (% D) in the samples withdrawn from the reaction mixture. The ir spectrum of each of several mixtures composed of weighted amounts of α-deuterated and nondeuterated *trans*-cinnamonitrile was recorded using no solvent in sodium chloride cells (0.025 cm thickness). The transmittance T at 975 cm^{-1} (due to the C=CH bond) and the transmittance T' at 955 cm^{-1} (due to the C=CD bond) were determined. The % D of each of the same samples was determined from their mass spectra. A standard curve for the quantitative ir analysis was prepared by plotting log T/T' against % D. Solvents (ethyl [^{2}H]alcohol and acetic acid) were evaporated from each of the quenched samples withdrawn from the reaction mixture and the residue was distilled under vacuum into a cooled trap. This distillate consisted of a mixture of the addition product of ethyl [^{2}H]alcohol to *trans*-cinnamonitrile and the α-deuterated and nondeuterated olefins. The ir spectrum of the liquid was recorded, log T/T' determined, and the % D then directly read from the standard curve.

Registry No.—Ethyl [^{2}H]alcohol, 925-93-9; *trans*-cinnamonitrile, 1885-38-7; sodium ethoxide, 141-52-6; *cis*-cinnamonitrile, 24840-05-9.

Supplementary Material Available. Figures 3, 4, and 5 and Table II describing the addition of ethyl [^{2}H]alcohol to *trans*- and *cis*-cinnamonitrile (4 pages). Ordering information is given on any current masthead page.

References and Notes

(1) C. A. Fyfe, "The Chemistry of the Hydroxyl Group", S. Patai, Ed., Interscience, New York, N.Y., 1971, p 62.
(2) B. A. Feit and A. Zilkha, *J. Org. Chem.*, **28**, 3245 (1963).
(3) R. N. Ring, G. G. Tesoro, and R. R. Moore, *J. Org. Chem.*, **32**, 1091 (1967).
(4) B. A. Feit and Z. Bigon, *J. Org. Chem.*, **34**, 3942 (1969).
(5) W. G. Davies, E. W. Hardisty, T. P. Nevell, and R. H. Peters, *J. Chem. Soc. B*, 998 (1970).
(6) N. Ferry and F. McQuillin, *J. Chem. Soc.*, 103 (1962).
(7) P. Chamberlain and G. H. Whitham, *J. Chem. Soc. B*, 1131 (1969).
(8) R. Luft, S. Delattre, and J. Basso, *C. R. Acad. Sci., Ser. C*, **271**, 1623 (1970).
(9) R. Luft, S. Delattre, and J. E. Armando, *Bull. Soc. Chim. Fr.*, 1317 (1971).
(10) B. A. Feit and L. Bohor, *J. Chem. Soc., Perkin Trans. 2*, 1823 (1974).
(11) S. Patai and Z. Rappaport, "The Chemistry of Alkenes", S. Patai, Ed., Interscience, New York, N.Y., 1964, p 469.
(12) H. M. Walborsky and L. M. Turner, *J. Am. Chem. Soc.*, **94**, 2273 (1972).
(13) J. F. Arnett and H. M. Walborsky, *J. Org. Chem.*, **37**, 3678 (1972).
(14) B. A. Feit, L. Bohor, and S. Rubinraut, *J. Chem. Soc., Perkin Trans. 2*, 253 (1976).
(15) B. A. Feit, *Eur. Polym. J.*, **3**, 523 (1967).
(16) J. Shabtai and H. Pines, *J. Org. Chem.*, **30**, 3854 (1965).
(17) B. A. Feit and A. Zilkha, *J. Appl. Polym. Sci.*, **7**, 287 (1963).
(18) D. J. Cram and L. Gosser, *J. Am. Chem. Soc.*, **85**, 3696 (1963).
(19) R. Stewart, J. P. O'Donell, D. J. Cram, and B. Rickborn, *Tetrahedron*, **18**, 917 (1962).
(20) H. M. Walborsky and J. M. Motes, *J. Am. Chem. Soc.*, **92**, 2445 (1970).
(21) G. W. Koeppl, D. S. Sagatys, G. S. Krishnamurthy, and S. I. Miller, *J. Am. Chem. Soc.*, **89**, 3396 (1967).
(22) J. Goshes, *Bull. Soc. Chim. Belg.*, **41**, 477 (1932).
(23) C. N. R. Rao in "Chemical Applications of Infrared Spectroscopy", Academic Press, New York, N.Y., 1963, p 538.
(24) See paragraph at end of paper regarding supplementary material.

Regioselective Nucleophilic Addition to 3,4-Lutidine

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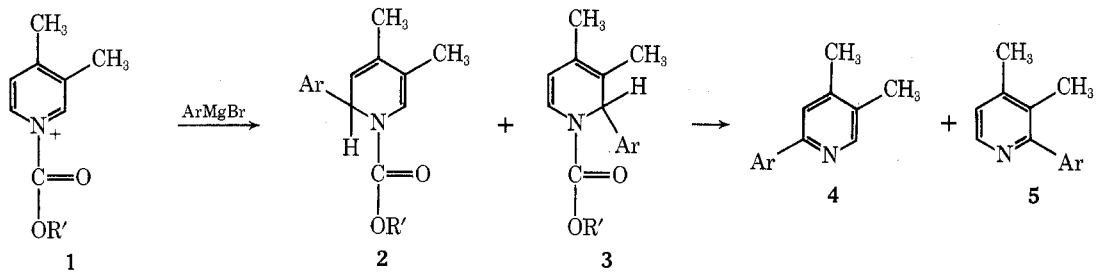
Received March 24, 1976

The usual orientation of nucleophilic addition at the 2 position of a 3-alkylpyridine can be changed by increasing the steric requirements of the nitrogen substituent. Thus the addition of phenylmagnesium bromide to the alkyl chloroformate ester salts of 3,4-lutidine is regioselective giving up to 90% addition of the aryl group at the 6 position. The large steric requirements of the 1-phenoxycarbonyl group or an ortho-substituted phenyl Grignard reagent gave 95% or greater regioselectivity of reaction at the less hindered α position of the 3,4-lutidine salt.

The reactions of nucleophiles with pyridines and pyridine derivatives may occur by addition at the 2, 4, or 6 position of the ring.[1] When the nucleophile is an organometallic reagent the addition usually takes place adjacent to the nitrogen, at the 2 or 6 positions,[2] and with the unsymmetrical ring having a 3-alkyl group, the addition is primarily at the 2 position.

Table I



1 2 3

Compd	R'	Ar	4/5	Overall yield, %	Solvent
a	CH_3CH_2	C_6H_5	78/22	31	Ether
b	i-C_4H_9	C_6H_5	75/25	27	THF
c	i-C_3H_7	C_6H_5	90/10	32	Ether
d	C_6H_5	C_6H_5	92/8	35	THF
e	CH_3CH_2	p-ClC_6H_4	62/38	40	THF
f	C_6H_5	p-ClC_6H_6	95/5	55	THF
g	CH_3CH_2	o-$CH_3C_6H_4$	95/5	46	THF
h	C_6H_5	o-$CH_3C_6H_4$	>95[a]	56	THF

[a] Only a trace of **5** could be detected in the NMR spectrum.

Thus the reactions of phenyllithium with 3-picoline,[3] 3-alkyl-1-ethoxypyridinium bromides with Grignard reagents,[4] and 3,4-lutidine methiodide with benzylmagnesium chloride[2c,5] all give as the sole or major product compounds resulting from addition of the organometallic reagent at the 2 position. This unexpected regiospecificity has been rationalized as resulting from an "ortho" effect of the 3-alkyl group probably related to London forces.[3]

The requirement for a series of 2-aryl-4,5-lutidines for a synthetic problem in this laboratory would be facilitated if the regiospecificity of the addition of an organometallic reagent to a 3,4-lutidine derivative could be controlled to give predominently reaction at the less hindered, 6 position. To make use of this steric factor to govern the regiospecificity of the nucleophilic addition it was evident from the literature that a group with large steric requirements would have to be introduced on the nitrogen. Since the pyridines were the desired product, the nitrogen substituent must be easily lost in the aromatization of the intermediate dihydropyridine. The activation of the pyridine ring to reaction with a Grignard reagent by salt formation with a chloroformate, recently reported by Fraenkel and co-workers[6] with 4-substituted pyridines, seemed to provide a possible method for controlling the regiospecificity.

The steric requirements of the nitrogen substituent were varied by changing the nature of the alkyl group of the ester of the chloroformate, and the various 1-alkoxycarbonyl-3,4-lutidinium salts (1) were treated with an aryl Grignard reagent. The NMR spectrum of the mixture of 1-alkoxycarbonyl-2-aryl-1,2-dihydro-3,4-lutidine (**3**) and 1-alkoxycarbonyl-2-aryl-1,2-dihydro-4,5-lutidine (**2**) was not resolved sufficiently to allow analysis of the product. Thus aromatization of the mixture by heating with sulfur gave the pyridines **4** and **5** which could be analyzed by the NMR. The results of the study are given in Table I.

Results and Discussion

The reaction of 3,4-lutidine with the chloroformates gave the salts which in turn were treated with a Grignard reagent to give a mixture of dihydropyridines (**2** and **3**). Except for the product from the reaction of p-chlorophenylmagnesium bromide and the phenyl chloroformate salt of 3,4-lutidine, which was largely the solid 1-phenoxycarbonyl-2-p-chlorophenyl-4,5-dimethyl-1,2-dihydropyridine (**2f**), the oily mixtures of dihydropyridines were not analyzed. The products were aromatized by heating with sulfur rather than by reaction with n-butyllithium, the procedure previously described,[6] since the former procedure is more convenient for preparative scale reactions.

The reactions of unhindered aryl Grignard reagents with the lutidine salts from ethyl and isobutyl chloroformate, alkyl groups with no branching near the carbonyl group, gave significant amounts of reaction at the 2 position of the pyridine ring (**1a,b,e**). The alkoxycarbonyl salts of 3,4-lutidine (**1**) gave a much greater ratio of addition of the aryl Grignard reagent at the 6 position than did other derivatives of 3,4-lutidine or the base itself. An increase in the steric requirements of the ester (**1c,d,f**) or in the Grignard reagent (**g**) gave much greater regioselectivity with nearly exclusive reaction at the 6 position. Thus with the hindered Grignard reagent, o-tolylmagnesium bromide, even the smallest ester, ethoxycarbonyllutidinium salts, gave nearly exclusively a single isomer. This orientation is particularly noteworthy when compared with the reaction of o-tolyllithium or o-ethylphenyllithium with 3-picoline which was reported to give about 95% addition at the 2 position.[7] Similar high regiospecificity was achieved with any aryl Grignard reagent with the phenyl chloroformate salt of 3,4-lutidine.

These results clearly show that orientation of nucleophilic arylation of 3-alkylpyridines can be controlled to give substitution at the position ortho to the alkyl group using the base or by using *our* procedure to give substitution "para" to the alkyl substituent.

Experimental Section

Melting points were determined using a Thomas-Hoover capillary melting point apparatus or a Mel-Temp apparatus and were not corrected for thermometer stem exposure. Elemental analyses were determined using an F and M Model 185 C, H, and N analyzer. Infrared spectra were determined using Perkin-Elmer Model 137 or 337 spectrometers with samples prepared as mulls or KBr pellets. The nuclear magnetic resonance spectra were determined using a JEOL Model MH-100 spectrometer.

2-Aryl-3,4- and -4,5-dimethylpyridines (4 and 5). A solution of 3,4-lutidine (5.36 g, 0.05 mol) in 150 ml of dry THF (ether) under nitrogen was cooled in a carbon tetrachloride–dry ice bath. An alkyl chloroformate (0.05 mol) was added dropwise over 5 min to the stirred solution, forming a white precipitate. An aryl Grignard reagent (0.06 mol) in 55 ml of THF (ether) was then added dropwise at such a rate as not to allow the temperature to rise above 0 °C. After the addition was completed, the mixture was stirred at 0–5 °C (ice bath) for 1 h and hydrolyzed with 50 ml of 20% ammonium chloride solution. The or-

ganic layer was washed with 50-ml portions of 5% NaOH, water, 5% HCl, water, and brine, and then was dried (K_2CO_3). Evaporation of the solvent gave yellow oils as a residue which were treated with 1 equiv of sublimed sulfur at 190–200 °C for 45 min. The reaction mixture was cooled, dissolved in 150 ml of ether, and extracted with three 50-ml portions of 10% hydrochloric acid. The acid extracts were washed with 50 ml of ether, made basic with 20% NaOH, and extracted with four 50-ml portions of ether. The organic layer was washed with brine and dried (K_2CO_3). The solution was filtered and concentrated and the residue was distilled, giving a mixture of 2-aryl-3,4-dimethylpyridine (**5**) and 2-aryl-4,5-dimethylpyridine (**4**). The percentages of the isomeric pyridines **4** and **5** were determined from the NMR spectrum of the mixture. The combined quantities of **4** and **5** were given from the integration of the signal for the α protons which were accidentally identical at δ 8.54 for Ar = C_6H_5 or p-ClC_6H_4 or at δ 8.64 for Ar = o-$CH_3C_6H_4$. The relative amount of **5** in the mixture was obtained from the integration of the signal for the 5 proton, a doublet at δ 7.14 for Ar = p-ClC_6H_4 or o-$CH_3C_6H_4$ or at δ 7.08 for Ar = C_6H_5.

1-Phenoxycarbonyl-2-*p*-chlorophenyl-4,5-dimethyl-1,2-dihydropyridine (2f). A solution of 3,4-lutidine (10.71 g, 0.1 mol) in 200 ml of dry THF under nitrogen was cooled in a carbon tetrachloride–dry ice bath. Phenyl chloroformate (15.66 g, 0.1 mol) was added dropwise over 5 min to the stirred solution giving a white precipitate. A solution of p-chlorophenylmagnesium bromide (0.12 mol) in 100 ml of THF was added dropwise at a rate which kept the temperature below 0 °C. After the addition was completed, the mixture was stirred at 0–5 °C (ice bath) for 1 h and then was hydrolyzed with 100 ml of 20% NH_4Cl solution. The organic layer was washed with 50 ml of 5% NaOH solution and 50 ml of saturated brine solution and then was dried (K_2CO_3) and evaporated. The residual yellow oil crystallized on standing under pentane to give 25.7 g (76%) of **2f** as a light yellow solid. The product was recrystallized twice from isopropyl alcohol to give an analytical sample of **2f:** mp 111–114 °C; NMR ($CDCl_3$) δ 7.08–7.80 (m, 9 H), 6.92 (br s, 1 H), 6.03 (d, 1 H), 5.68 (d, 1 H), 1.70–2.08 (2 s, 6 H); ir (KBr) 1705 cm^{-1}.

Anal. Calcd for $C_{20}H_{18}ClNO_2$: C, 70.69; H, 5.34; N, 4.12. Found: C, 70.95; H, 5.26; N, 4.07.

2-Phenyl-4,5-dimethylpyridine (4d). A solution of 3,4-lutidine (5.36 g, 0.05 mol) in 150 ml of dry THF under nitrogen was cooled in a carbon tetrachloride–dry ice bath. Phenyl chloroformate (7.83 g, 0.05 mol) was added dropwise over 5 min to the stirred solution, forming a white precipitate. A solution of phenylmagnesium bromide (0.06 mol) in 55 ml of THF was added dropwise at a rate to keep the temperature below 0 °C. After the addition was complete, the mixture was stirred at 0–5 °C (ice bath) for 1 h and then was hydrolyzed with 50 ml of 20% NH_4Cl solution. The organic layer was washed with 50-ml portions of 5% NaOH, water, 5% HCl, water, and brine, and then was dried (K_2CO_3). The mixture was filtered and evaporated to yield 12.32 g of a yellow oil. The crude yellow oil was treated with sublimed sulfur (1.29 g, 40.37 mmol) at 190–200 °C for 45 min. The reaction mixture was cooled, dissolved in 150 ml of ether, stored over sodium hydroxide pellets overnight, and filtered. The filtrate was washed with 50 ml of 10% sodium hydroxide and 50 ml of water, and was extracted with three 50-ml portions of 10% hydrochloric acid. The acid extracts were washed with 50 ml of ether, made basic with 20% sodium hydroxide and extracted with four 50-ml portions of ether. The organic layer was washed with water and brine and was dried (K_2CO_3). The solution was filtered, concentrated, and distilled, giving 3.23 g (35%) of **4d** as a light yellow oil: bp 117–120 °C (0.35 mm); picrate mp 203–204 °C [lit.[8] bp 146–150 °C (6 mm), picrate mp 202–203 °C]; NMR ($CDCl_3$) δ 8.58 (s, 1 H), 8.12–8.28 (m, 2 H), 7.44–7.70 (m, 4 H), 2.16 (s, 6 H).

2-*p*-Chlorophenyl-4,5-dimethylpyridine (4f). A mixture of 15.0 g (44.14 mmol) of crude **2f** and 1.27 g (39.73 mmol) of sublimed sulfur was heated with stirring at 190–200 °C for 45 min. The reaction mixture was cooled, dissolved in 150 ml of ether, and placed over sodium hydroxide pellets overnight. The solution was filtered and washed with 50 ml of 20% sodium hydroxide solution and 50 ml of water. The solution was extracted with three 50-ml portions of 10% hydrochloric acid. The acid extracts were filtered, washed with 25 ml of ether, made basic with 20% sodium hydroxide, and extracted with four 50-ml portions of ether. The ether extracts were washed with saturated brine solution, dried (K_2CO_3), and evaporated to give a brown solid. Distillation of the solid (bp 125–130 °C, 0.06 mm) yielded 6.9 g (72%) of **4f** as a light yellow solid. The solid was recrystallized twice from hexane–Norite to give **4f** as white crystals: mp 61.5–62 °C; NMR ($CDCl_3$) δ 8.48 (s, 1 H), 8.00 (d, 2 H), 7.46 (d, 2 H), 7.43 (s, 1 H), 2.20 (s, 6 H).

Anal. Calcd for $C_{13}H_{12}ClN$: C, 71.72; H, 5.56; N, 6.43. Found: C, 71.71; H, 5.65; N, 6.56.

2-(*o*-Tolyl)4,5-dimethylpyridine (4g). Using the procedure for the preparation of **4f,** 10.71 g (0.1 mol) of 3,4-lutidine, 11.19 g (0.1 mol) of ethyl, chloroformate, and 0.12 mol of o-tolylmagnesium bromide in 100 ml of THF gave, after vacuum distillation, 16.2 g of a yellow oil. Treatment with 1.91 g (59.7 mmol) of sublimed sulfur gave, after vacuum distillation, 9.0 g (46%) of a yellow oil. The oil was treated with Norite–chloroform and redistilled to give an analytical sample of **4g:** bp 110–115 °C (0.35 mm); picrate, mp 166–167 °C; NMR ($CDCl_3$) δ 8.64 (s, 1 H), 7.35–7.68 (m, 4 H), 7.30 (s, 1 H), 2.43 (s, 3 H), 2.24 (s, 6 H).

Anal. Calcd for $C_{14}H_{15}N$: C, 85.24; H, 7.66; N, 7.10. Found: C, 85.28; H, 7.65; N, 7.12.

Acknowledgment. The authors wish to express appreciation to the National Cancer Institute of the NIH for partial support of this project from Grant CA-12149. One author, D.L.C., further expresses appreciation to the Graduate School of the University of New Hampshire for a Summer Fellowship for Graduate Teaching Assistants. The authors also wish to thank Reilly Tar and Chemical for a generous supply of 3,4-lutidine.

Registry No.—2f, 59463-69-3; **4d,** 27063-84-9; **4d** picrate, 27063-85-0; **4f,** 59463-70-6; **4g,** 59463-71-7; 3,4-lutidine, 583-58-4; phenyl chloroformate, 188-14-9; p-chlorophenyl bromide, 106-39-8; phenyl bromide, 108-86-1; o-tolyl bromide, 95-46-5; ethyl chloroformate, 541-41-3.

References and Notes

(1) R. A. Abramovitch and G. M. Singer in "Pyridine and Its Derivatives", Vol. 14, Part 1, R. A. Abramovitch, Ed., Wiley-Interscience, New York, N.Y., 1974, p 45.
(2) (a) R. E. Lyle in ref 1, p 147; (b) U. Eisner and J. Kuthan, *Chem. Rev.*, **72,** 1 (1972); (c) "Synthetic Analgesics", J. Hellerbach, O. Schnider, H. Besendorf, and B. Pellmont, Part IIA, "Morphinans", and N. B. Eddy and E. L. May, Part IIB, "6,7-Benzomorphans", Pergamon Press, Oxford, 1966, pp 117–137; (d) R. E. Lyle and E. White V, *J. Org. Chem.*, **36,** 772 (1971).
(3) (a) Reference 1, p 50; (b) R. A. Abramovitch and J. G. Saha, *Adv. Heterocycl. Chem.*, **6,** 229 (1966); (c) R. A. Abramovitch and C. S. Glam, *Can. J. Chem.*, **42,** 1627 (1969).
(4) O. Cervinka, *Chem. Ind. (London)*, 1482 (1960).
(5) (a) Reference 3b, p 304; (b) M. Alverez, J. Bosch, and J. Canak, *An. Quim.*, **71,** 807 (1975).
(6) G. Fraenkel, J. W. Cooper, and C. M. Fink, *Angew. Chem., Int. Ed. Engl.* **9,** 523 (1970).
(7) R. A. Abramovitch, C. S. Glam, and G. A. Poulton, *J. Chem. Soc. C,* 128 (1970).
(8) G. J. Janz, and W. J. H. McCulloch, *J. Am. Chem. Soc.*, **77,** 3143 (1955).