zation and the rate of proton transfer to decrease and the amount of ion pairing to increase. All of these could contribute to the observed increase in line width. In concentrated aqueous hydrochloric acid, however, proton transfer rates would still be high because of the high proton concentration, but the same high proton concentration would cause the sulfonic acid to ionize less, and the $^{33}S$ line width would increase. Thus, the degree of ionization appears to be the most important factor in determining the $^{33}S$ line widths of sulfonic acids. Clearly, $^{33}S$ NMR is a novel way to study the solution properties of sulfonic acids, and we are continuing our studies in this area.

## Experimental Section

**Instrumental.** All spectra were run on a standard Varian 24K FT-80 spectrometer equipped with a 10-mm broad-band probe. During the course of this work the signal to noise ratio was significantly improved by the addition of a new preamplifier and quarter wavelength filter from Varian. Most of the spectra were acquired with an 8-kHz window, but, to avoid possible folding of spectra, preliminary work was done with a 20-kHz window using an Ithaco 4302 audio filter in the low pass mode and the program WIDESW obtained from Steve Patt. The standard conditions for 8-kHz spectra were the following: a 70-$\mu$s pulse (90°); a 0.05-s acquisition time; a 1500-$\mu$s $\alpha$ delay between pulse and acquisition; no proton decoupling; 40 000 to $1 \times 10^6$ transients; and external lock. The choice of 1500 $\mu$s for the $\alpha$ delay is a compromise between signal to noise ratio and base-line roll.[11] It should be noted that apparent line width is limited by acquisition time: a very narrow line such as ammonium sulfate requires a longer acquisition time. All chemical shift values are reported with reference to external 4 M ammonium sulfate[1a,12] since the broader line of carbon disulfide[2,3] afforded less precision in the measurements. We also discovered that spinning the sample made little difference with line widths of over 10 Hz. In preliminary studies, there was a decrease of line width with increased temperature, so we ran most spectra at temperatures around 40 °C. The temperature of the probe varied with the temperature of the cooling water, so temperatures were measured with a mercury thermometer positioned against the probe.

**Compounds.** Samples were commercially available from Aldrich, Eastman, or Mallinckrodt or have been prepared by previously reported procedures. Physical properties such as IR spectra and melting points were consistent with those previously reported. Spectroscopic samples were prepared by dissolving approximately 1.0 g of compound in sufficient deionized water or other specified solvent to make a 2.0 mL volume. If the solution was not complete, solvent was added as necessary to effect solution. Actual concentrations are listed in Table I. A number of compounds could not be run because of solubility problems. When no signal was seen, a C-13 spectrum was generally run to check the sample. The pH values were measured with pHydrion paper.

**Acknowledgment.** We thank Bob Santini of Purdue University for help with the audio filter and Prof. L. Sousa of Ball State for allowing us to run comparison spectra on an FT-80a spectrometer.

**Registry No.** $MeSO_3H$, 75-75-2; $NH_2NH(CH_2)_2SO_3^-\cdot Na^+$, 62716-44-3; $Br(CH_2)_2SO_3^-\cdot Na^+$, 4263-52-9; $CH_2{=}CHCH_2SO_3^-\cdot Na^+$, 2495-39-8; $PhSO_3H$, 98-11-3; $p$-$MeC_6H_4SO_3H$, 104-15-4; $d$-camphor-10-sulfonic acid, 3144-16-9; mesitylenesulfonic acid, 3453-83-6; $\alpha$-naphthalenesulfonic acid, 85-47-2; 4-aminotoluene-2-sulfonic acid, 118-88-7; sulfosalicylic acid, 97-05-2; sodium 2-benzaldehydesulfonate, 1008-72-6; disodium $m$-benzenedisulfonate, 831-59-4; dipotassium $o$-benzenedisulfonate, 5710-54-3.

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## Regiospecific $\alpha$-Alkylation of 4-Chloro(bromo)pyridine

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Halopyridines have been widely used as intermediates in synthetic sequences. The 4-halopyridines are particularly useful as they undergo a wide variety of substitution reactions. Nucleophilic substitution of 4-halopyridines is an important method for the introduction of a wide range of oxygen, sulfur, nitrogen, and carbon substituents.[1] This approach to 4-substituted pyridines is limited, however, by the availability of substituted 4-halopyridines. Generally, the 4-halopyridines are prepared from 4-pyridone or 4-aminopyridine precursors, which frequently require multistep synthesis.[2] Since 4-chloro- and 4-bromopyridine are commercially available as their hydrochloride salts, it seemed desirable to explore ring $\alpha$-alkylation of these compounds as a short and convenient route to $\alpha$-substituted 4-halopyridines.

The Grignard addition to 1-acylpyridinium salts has proven to be a convenient method for the synthesis of substituted dihydropyridines and pyridines.[3] We chose to examine the reaction of Grignard reagents with the 1-phenoxycarbonyl salt of 4-chloropyridine. Initially we were concerned that displacement of halogen from the 1-(phenoxycarbonyl)-4-chloropyridinium ion **1** might occur instead of $\alpha$-addition, since methoxide ion reacts faster with *N*-methyl-4-chloropyridinium ion than with 4-chloropyridine by roughly a factor of $10^{10}$.[4] However, substitution of the halogen was not a problem as the Grignard reagent added to the $\alpha$-position in high yield to give dihydropyridines **2**. Aromatization of crude **2** with $o$-chloranil in toluene/acetic acid gave the desired 2-alkyl-4-chloropyridines **3** in moderate overall yield as shown in Table I.

The analogous sequence using 1-(phenoxycarbonyl)-4-bromopyridinium chloride provides 2-substituted 4-bromopyridines. The free base of 4-bromopyridine hydrochloride is rather unstable at room temperature, however, so the first step is best carried out by neutralizing the hydrochloride salt in situ with Grignard reagent. We found it most convenient to add 2 equiv of the Grignard reagent to a slurry of 4-bromopyridine hydrochloride (**4**) in THF at −78 °C, followed by the dropwise addition of phenyl chloroformate. The resulting dihydropyridine can

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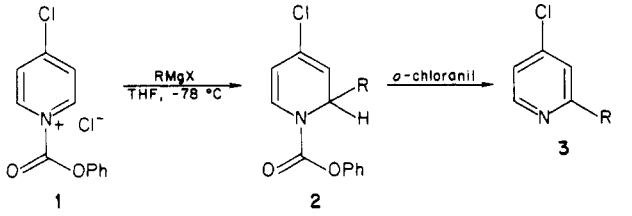
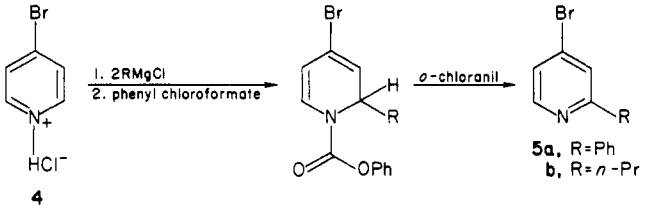
**Table I. Synthesis of 2-Alkyl-4-chloropyridines 3**




| RMgX[a] | yield of 3,[b] % | deriv[c] mp (lit. mp), °C |
|---|---|---|
| $n$-$C_3H_7MgCl$ | 46 | hydrochloride 130.5–132 |
| $C_6H_{11}MgCl$ | 36 | picrate 124–124.5 |
| $C_6H_5MgCl$ | 55 | picrate 183–184 (180)[5] |
| $C_2H_5MgBr$ | 46 | hydrochloride 193–194 (179–180)[6] |
| $n$-$C_6H_{13}MgBr$ | 64 | tetraphenylborate[d] 129–131 |
| $C_2H_3MgBr$ | 54 | hydrochloride 184–184.5 |
| 1-$C_{10}H_7MgBr$ | 53 | 95–96 |
| $(CH_3)_2CHMgCl$ | 42 | hydrobromide 168.5–169.5 |

[a] The reactions were performed on a 3-mmol scale in THF. [b] Yield of purified product obtained from radial preparative layer chromatography. All products gave the expected IR and $^1H$ NMR spectra. Satisfactory analytical data (±0.4% for C, H, N) were obtained for all new compounds listed in the table. [c] Unless indicated, the derivatives were recrystallized from 2-propanol. [d] The tetraphenylborate was not recrystallized.

be aromatized with *o*-chloranil. This procedure was utilized for the synthesis of 4-bromo-2-phenylpyridine (**5a**) and 4-bromo-2-*n*-propylpyridine (**5b**) in overall yields of 50% and 59%, respectively.




## Experimental Section

Reactions involving organometallic reagents were performed in oven-dried glassware under a $N_2$ atmosphere. Tetrahydrofuran (THF) was dried by distillation from sodium benzophenone ketyl prior to use. Other solvents and reagents from commercial sources were generally used without further purification.

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. $^1H$ NMR spectra were recorded on a Varian EM-360 spectrometer. Elemental analyses were carried out by M-H-W Laboratories.

**4-Chloro-2-ethylpyridine. General Procedure.** To a cooled (−78 °C) solution of 4-chloropyridine (360 mg, 3.17 mmol) in 10 mL of THF was added an ethereal solution of ethylmagnesium bromide (3.49 mmol) in one portion. Immediately following, phenyl chloroformate (0.41 mL, 3.17 mmol) was added dropwise. The mixture was stirred at −78 °C for 10 min, allowed to come to room temperature, and quenched with aqueous 20% $NH_4Cl$ solution (10 mL). Ether (10 mL) was added, and the organic layer was washed with 10-mL portions of water, 10% HCl, water, and brine. After drying ($MgSO_4$), the solution was concentrated to give 1.46 g of the crude dihydropyridine as a yellow oil, which was dissolved in 15 mL of dry toluene. To this solution, at room temperature, was added dropwise *o*-chloranil (860 mg, 3.5 mmol) in 7 mL of glacial acetic acid. The mixture was stirred at room temperature for 24 h, cooled, and made basic with 10% NaOH. The mixture was stirred for 15 min and filtered through Celite. The dark organic layer was washed with water and then extracted with 3 × 10 mL of 10% HCl. The combined acid extracts were cooled, made basic with 20% NaOH, and extracted with methylene chloride (3 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and concentrated to yield the crude product (260 mg) as a yellow oil. Purification by radial preparative layer chromatography (EtOAc/hexanes) gave 207 mg (46%) of 4-chloro-2-ethylpyridine as a clear oil: IR (neat) 2950, 1580, 1470, 1100 $cm^{-1}$; $^1H$ NMR ($CCl_4$) δ 1.3 (t, 3 H), 2.82 (q, 2 H), 7.13 (d, 1 H), 7.2 (s, 1 H), 8.5 (d, 1 H). The hydrochloride salt was prepared for elemental analysis: mp 193–194 °C (2-propanol or methanol) lit.[6] [mp 179–180 °C (methanol)]. Anal. Calcd for $C_7H_9Cl_2N$: C, 47.22; H, 5.09; N, 7.87. Found: C, 47.24; H, 5.27; N, 8.02.

**4-Bromo-2-phenylpyridine.** To a slurry of 4-bromopyridine hydrochloride (590 mg, 3.03 mmol) in 10 mL of THF at −78 °C was added phenylmagnesium chloride (6.67 mmol) in 3.3 mL of THF. After stirring for 10 min at −78 °C, phenyl chloroformate (0.40 mL, 3.03 mmol) was added dropwise. The mixture was stirred at −78 °C for 10 min, warmed to room temperature, and quenched with aqueous 20% $NH_4Cl$ solution. Isolation of the dihydropyridine intermediate and subsequent aromatization with *o*-chloranil was as described above. Purification by radial preparative layer chromatography (10% EtOAc/hexane) gave 357 mg (50%) of 4-bromo-2-phenylpyridine as a clear oil: picrate mp 174.5–176 °C; IR (neat) 3120, 1560, 1380, 1045; $^1H$ NMR ($CCl_4$) δ 7.25–7.65 (m, 4 H), 7.85–8.25 (m, 3 H), 8.53 (d, 1 H). Anal. Calcd for $C_{11}H_8BrN$: C, 56.43; H, 3.44; N, 5.98. Found: C, 56.36; H, 3.52; N, 6.04.

**4-Bromo-2-*n*-propylpyridine.** The crude product was obtained from 4-bromopyridine hydrochloride and *n*-propylmagnesium chloride by using the procedure described above for the preparation of 4-bromo-2-phenylpyridine. Purification by radial preparative layer chromatography (25% EtOAc/hexane) gave 414 mg (59%) of 4-bromo-2-*n*-propylpyridine as a clear oil: hydrobromide mp 137.5–139 °C (sublimed); IR (neat) 2960, 1575, 1470, 1390, 1095; $^1H$ NMR ($CCl_4$) δ 0.93 (t, 3 H), 1.7 (m, 2 H), 2.69 (t, 2 H), 7.25 (m, 2 H), 8.32 (d, 1 H). Anal. Calcd for $C_8H_{11}Br_2N$ (hydrobromide): C, 34.19; H, 3.95; N, 4.98. Found: C, 34.46; H, 4.08; N, 4.87.

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**Registry No.** 1, 98420-84-9; 2 (R = $C_2H_5$), 98420-85-0; 2 (R = $C_6H_5$, 4-bromo-analogue), 98420-86-1; 3 (R = $n$-$C_3H_7$), 93856-98-5; 3 (R = $n$-$C_3H_7$)·HCl, 98420-92-9; 3 (R = $C_6H_{11}$), 98420-87-2; 3 (R = $C_6H_{11}$)·picrate, 98420-93-0; 3 (R = $C_6H_5$), 57311-18-9; 3 (R = $C_6H_5$)·picrate, 98420-94-1; 3 (R = $C_2H_5$), 3678-65-7; 3 (R = $C_2H_5$)·HCl, 98420-95-2; 3 (R = $n$-$C_6H_{13}$), 98420-88-3; 3 (R = $n$-$C_6H_{13}$)·$HBPh_4$, 98421-01-3; 3 (R = $C_2H_3$), 98420-89-4; 3 (R = $C_2H_3$)·HCl, 98420-96-3; 3 (R = 1-$C_{10}H_7$), 98420-90-7; 3 (R = $CH(CH_3)_2$), 98420-91-8; 3 (R = $CH(CH_3)_2$)·HBr, 98420-97-4; 4, 19524-06-2; **5a**, 98420-98-5; **5b**, 98420-99-6; **5b**·HBr, 98421-00-2; PhOCOCl, 1885-14-9; $n$-$C_3H_7Cl$, 540-54-5; $C_6H_{11}Cl$, 542-18-7; $C_6H_5Cl$, 108-90-7; $C_2H_5Br$, 74-96-4; $n$-$C_6H_{13}Br$, 111-25-1; $C_2H_3Br$, 593-60-2; 1-$C_{10}H_7Br$, 90-11-9; $(CH_3)_2CHCl$, 75-29-6; 4-chloropyridine, 626-61-9; *o*-chloranil, 2435-53-2.