Table IV. Coordinates for (Aza-12-crown-4)$_2$•NaI

atom	x	y	z
I	0.79062 (1)	x	0
Na	0.43313 (8)	x	0
O1	0.3036 (1)	0.6568 (2)	0.00259 (8)
O2	0.1935 (2)	0.4104 (2)	0.03122 (10)
O3	0.4148 (2)	0.3453 (2)	0.10192 (8)
N	0.5290 (2)	0.5933 (2)	0.07463 (9)
C1	0.4493 (3)	0.7095 (3)	0.0850 (1)
C2	0.3864 (3)	0.7545 (2)	0.0280 (1)
C3	0.1767 (3)	0.6493 (3)	0.0291 (2)
C4	0.1170 (3)	0.5200 (4)	0.0121 (2)
C5	0.1784 (3)	0.3779 (4)	0.0921 (2)
C6	0.2882 (4)	0.2872 (3)	0.1093 (1)
C7	0.4478 (4)	0.4345 (3)	0.1480 (1)
C8	0.5618 (3)	0.5182 (3)	0.1277 (1)

used. Refinement was carried out by full-matrix least squares based on F with weights $w = \sigma^{-2}(F\sigma)$, treating non-hydrogen atoms anisotropically. Hydrogen atoms were located by difference maps and refined isotropically. Convergence was obtained (Δ/ρ maximum = 0.04) in $P4_32_12$ with agreement factors listed above. Seven reflections had ΔF greater than $5\sigma(F)$, none greater than $7\sigma(F)$. Refinement under identical conditions in $P4_12_12$ yielded $R = 0.033$, $R_w = 0.038$, GOF = 1.926, 51 reflections with $\Delta F > 5\sigma(F)$, and five reflections with $\Delta F > 8\sigma(F)$. The difference in R_w is significant at better than $\alpha = 0.005$ by the Hamilton R factor ratio test.[27] Coordinates for the correct configuration are listed in Table IV.

Acknowledgment. We warmly thank the National Institutes of Health (G.W.G.), W. R. Grace & Co. (G.W.G.), and the Donors of the Petroleum Research Fund, administered by the American Chemical Society (R.L.G.) for support of this work.

Supplementary Material Available: Anisotropic thermal parameters for $(C_8H_{17}NO_3)_2$·NaI, coordinates and isotropic thermal parameters for hydrogen atoms of $(C_8H_{17}NO_3)_1$·NaI, projection of the structure along the c axis, and view of the unit cell slightly oblique to the b axis, with c vertical (4 pages). Ordering information is given on any current masthead page.

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Regioselective Functionalization of Pyridinesulfonic Acids. Ortho-Lithiation of Tertiary 2- and 4-Pyridinesulfonamides

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Tertiary 2- and 4-pyridinesulfonamides were ortho-lithiated at low temperature by an excess of lithium diisopropylamide. Proton abstraction occurs selectively at the more acid 3-positions in the two cases. 3-Lithio-2- and -4-(piperidinosulfonyl)pyridines reacted with such electrophiles as iodine, aldehydes, 3-pentanone, dimethylformamide, and carbon dioxide to give the corresponding ortho-disubstituted pyridines in high yields. Lithiation ability of the pyridinesulfonamides was also compared with that of the benzene analogue.

Electron-rich heteroaromatics such as pyrrole, furan, and thiophene easily undergo electrophilic substitution. However, this powerful synthetic tool can seldom be used with electron-deficient heteroaromatic compounds such as pyridine and quinoline. Metalation is another powerful and regioselective method for substituting aromatic derivatives,[1] but it has only recently been applied to pyridines[2] because of the peculiar reactivity of the pyridine ring toward nucleophilic metalating agents such as chelated alkyllithiums. A proper choice of reaction conditions allows the directed lithiation of pyridines that bear ortho-directing groups.[2]

Little work has been done on the metalation of compounds bearing a sulfur-containing substituent except for our recent short report on the metalation of tertiary 3-pyridinesulfonamides.[3] In the homoaromatic series,[4] a (*N*,*N*-dialkylamino)sulfonyl moiety is an effective ortho-directing group for metalation of sulfonic acids. These lithiations are carried out with nucleophilic chelated alkyllithiums, which are ineffective with pyridine analogues.[3,5] We report here on the metalation of 2- and 4-pyridinesulfonamides.

Results

2-[(*N*,*N*-Dialkylamino)sulfonyl]pyridines **1a–c** were prepared from commerical 2-pyridinethiol via 2-pyridinesulfonyl chloride.[6] 4-[(*N*,*N*-Dialkylamino)-sulfonyl]pyridines **2a–c** were obtained by a four-step sequence starting from commerical 4-nitropyridine *N*-oxide.[7]

Metalation of Pyridinesulfonamides. Lithiation of 2-pyridinesulfonamides **1a–c** was performed at low temperature by using an excess of lithium diisopropylamide (LDA). The 3-lithio derivatives **3a–c** were quenched with benzophenone at −70 °C to give **4a–c** in yields of 87–95%. Under similar conditions, 4-pyridinesulfonamides **2a–c** were substituted in the 3-position to give **6a–c**.

(1) For a general review of metalation, see: Wakefield, B. J. *The Chemistry of Organolithium Compounds*; Pergamon: Oxford, 1974. For a recent review of the scope of directed metalation, see: Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1.
(2) Marsais, F.; Queguiner, G. *Tetrahedron* **1983**, *39*, 2009.
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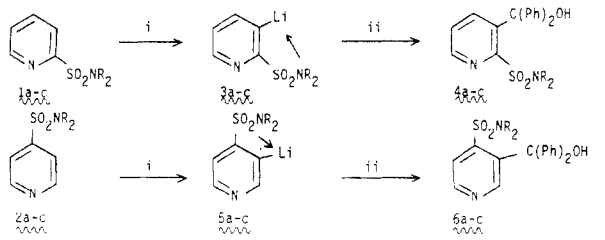
(6) 2-Pyridinesulfonyl chloride has been prepared by chlorination of 2-pyridinethiol.[7] Overall yields of **2a–c** are, respectively, 70%, 75%, and 80%.
(7) Ochiai, E. *J. Org. Chem.* **1953**, *18*, 538. Angulo, J.; Municio, A. M. *An. R. Soc. Esp. Fis. Quim., Ser. B.* **1960**, *56*, 395. The overall sequence is as follows: 4-chloropyridine *N*-oxide, 4-pyridinethiol *N*-oxide, 4-pyridinesulfonyl chloride *N*-oxide, and 4-[(*N*,*N*-dialkylamino)sulfonyl]-pyridine *N*-oxides. Overall yields of **1a–c** have been optimized to 50%, 35%, and 60%, respectively.

0022-3263/87/1952-1133$01.50/0

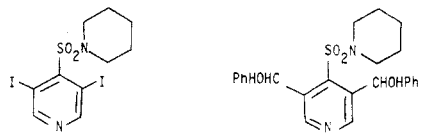
The best yield (95%) of purified **4a** was obtained from 2-(piperidinosulfonyl)pyridine (**1a**) by using 2 equiv of LDA in diethyl ether at −70 °C for 1.5 h.



a, $R_2 = (CH_2)_5$
b, $R_2 = (CH_2CH_2)_2O$
c, $R_2 = (CH_2)_4$

i : LDA/Et_2O/ − 70°C ; ii : Ph_2CO/ − 70°C

Lithiation of 4-(piperidinosulfonyl)pyridine (**2a**) proved to be highly sensitive to the amount of LDA and to the reaction time. It appears that reaction of **5a** with benzaldehyde or iodine produced small amounts of the corresponding 3,5-disubstituted sulfonamides **21** and **22** in addition to the 3-monosubstituted **14** and **16**.

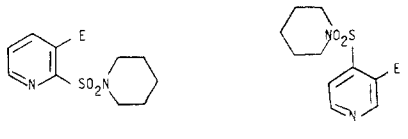


21 22

Metalation of **2a** with 3 equiv of LDA and reaction of benzaldehyde (3 equiv) for 3 h at −70 °C led to 32% of the 3,5-disubstituted product **22**. Under the same conditions, 2 equiv of LDA gave only 20% of **22**. The best monometalation selectivity was otained by using a twofold excess of LDA and reacting the electrophile at −70 °C for a half-hour. Deuteriolysis experiments excluded a 3,5-dilithio derivative, and one must suppose that 3-monosubstituted sulfonamides **14** and **16** were further lithiated by excess of LDA. This is due to the low reactivity of LDA toward iodine or benzaldehyde. Analogous 3,5-disubstituted derivatives were not isolated from reaction of **5a** with other electrophiles, and no disubstituted products were observed in reactions of **3a**.

Lithiated species **3a–c** and **5a–c** were white precipitates that were quite stable at low temperature.

Both lithiated compounds **3a** and **5a** reacted at −70 °C with such electrophiles as iodine, 3-pentanone, benzaldehyde, 2,4-dichlorobenzaldehyde, acetaldehyde, dimethylformamide, and carbon dioxide to give 3-substituted compounds **7–13** and **14–20**, respectively, in yields of 55–95%.

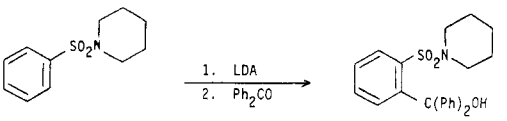


	E	
7	I	14
8	$C(C_2H_5)_2OH$	15
9	$CHOHC_6H_5$	16
10	$CHOHC_6H_3Cl_2$-2,4	17
11	$CHOHCH_3$	18
12	CHO	19
13	CO_2H	20

Secondary alcohols **9–11** and **16–18** were easily oxidized to the corresponding ketones **23–28** in quantitative yields with manganese dioxide in refluxing toluene.[8]

R		
23	C_6H_5	26
24	$C_6H_3Cl_2$-2,4	27
25	CH_3	28

We also compared the lithiation ability of a tertiary benzenesulfonamide with that of the pyridine analogues. (Piperidinosulfonyl)benzene (**29**)[9] reacted with 2 equiv of LDA in diethyl ether at −75 °C. Addition of benzophenone gave only a 5% yield of diphenyl[(piperidinosulfonyl)-phenyl]methanol (**30**). A higher lithiation yield was obtained by increasing the metalation temperature: 55% of tertiary alcohol **30** could be isolated after lithiation at 0 °C.



29 30

Experimental Section

The ^1H NMR spectra were obtained by using a Varian A 60 spectrometer and are recorded in ppm downfield of the internal standard of Me_4Si ($CDCl_3$) or HMDS (Me_2SO-d_6). ^1H–^1H coupling constants are in good agreement with the common values: $J_{2-3} \simeq 5$ Hz; $J_{3-4} \simeq 8$ Hz; $J_{2-4} \simeq 2$ Hz. IR spectra were obtained as potassium bromide dispersions from a Perkin-Elmer R-12 spectrometer. Wavenumbers are given for main absorptions (OH, C=O, C=C and C=N, SO_2—N. Elemental analyses were performed on a CHN Carlo Erba instrument.

Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from benzophenone/sodium and stored over 3-Å molecular sieves. The water content of the solvents was estimated by the modified Karl-Fischer method:[10] Et_2O < 10 ppm, THF < 45 ppm. Diisopropylamine, piperidine, morpholine, and pyrrolidine were redistilled from and stored over CaH_2.

Metalations were performed under a dry deoxygenated-argon atmosphere. The *n*-butyllithium (BuLi) content of the commercial hexane solution was estimated by the Gilman double titration method.

All compounds had ^1H NMR peaks in the vicinity of 1.60 (CH_2) and 3.30 (CH_2N). Satisfactory analyses (C, H, N) were obtained for all compounds.

Synthesis of 2- and 4-[(Dialkylamino)sulfonyl]pyridines. 4-[(Dialkylamino)sulfonyl]pyridine *N*-oxides were prepared by bubbling Cl_2 into a cold (−5 °C) solution of 4-mercaptopyridine *N*-oxide[7] (10 g, 0.08 mol) in 130 mL of 9 N HCl. The solution was neutralized by addition of $CaCO_3$ (10 g) at −5 °C, then of $CHCl_3$ (200 mL) and finally of $CaCO_3$ at −10 °C. The supernatant liquid was separated, and the remaining paste was washed twice with cold $CHCl_3$ (50 mL). The combined extracts were dried over $MgSO_4$ at 0 °C. The cold filtered solution was slowly aded at 0 °C to a mixture of the secondary amine (2 equiv, 0.16 mol) and $CHCl_3$ (100 mL). Stirring was continued for 1 h at 0 °C and 2 h at room temperature before washing with water (2 × 50 mL). Drying over $MgSO_4$ and solvent removal gave a solid, which was purified by crystallization from Et_2O. The 4-[(dialkylamino)-sulfonyl]pyridine *N*-oxides were reduced with hydrogen in CH_3OH

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(10) Bizot, J. *Bull. Soc. Chim. Fr.* **1967**, *1*, 151.

with Raney Ni catalyst (0.08 mol of *N*-oxide in 150 mL of CH_3OH and 40 g of Ni). The reactions were carried out at slightly over 1 atm and required about 5 h. Filtration over Celite and evaporation of CH_3OH gave quantitative yields of pure white solid.

2-[(Dialkylamino)sulfonyl]pyridines were prepared by the same procedure with commerical 2-mercaptopyridine as starting material.

2-(Piperidinosulfonyl)pyridine (1a): yield 70%; mp 59 °C; ^1H NMR ($CDCl_3$) δ 1.60 (m, 6 H, CH_2), 3.25 (m, 4 H, CH_2N), 7.50 (m, 1 H, H_5), 7.90 (m, 2 H, $H_3 + H_4$), 8.70 (dd, 1 H, H_6); IR 3090, 3050, 3000, 2980, 2960, 2940, 2920, 2850, 2845, 1575, 1560, 1465, 1450, 1435, 1425 cm^{-1}. Anal. Calcd for $C_{10}H_{14}N_2O_2S$: C, 53.08; H, 6.24; N, 12.38. Found: C, 53.1; H, 6.19; N, 12.3.

4-(Piperidinosulfonyl)pyridine (2a): yield 75%; mp 122 °C; ^1H NMR ($CDCl_3$) δ 1.55 (m, 6 H, CH_2), 3.00 (m, 4 H, CH_2N), 7.55 (d, 2 H, $H_3 + H_5$), 8.85 (d, 2 H, $H_2 + H_6$); IR 3100, 3060, 3040, 2960, 2880, 1570, 1550, 1460, 1450, 1400 cm^{-1}. Anal. Calcd for $C_{10}H_{14}N_2O_2S$: C, 53.08; H, 6.24; N, 12.38. Found: C, 53.0; H, 6.09; N, 12.2.

Lithiation of 2- and 4-[(Dialkylamino)sulfonyl]pyridines and Reactions with Electrophiles. *n*-Butyllithium (1.6 M in hexane, 15.5 mL, 0.025 mol) was slowly added to a solution of diisopropylamine (2.53 g, 0.025 mol) in Et_2O (50 mL) at −30 °C under argon. Stirring was continued for 1 h at 0 °C. The resulting mixture was cooled at −70 °C, and 2-[(dialkylamino)sulfonyl]-pyridine (0.0125 mol) in THF (30 mL) was added dropwise. After the mixture was allowed to stand at −70 °C for 1.5 h, a solution of the electrophile (0.025 mol) in THF (30 mL) was added. The mixture was allowed to stand for 3 h at −70 °C before hydrolysis at −70 °C (H_2O/THF, 1 mL/10 mL) and addition of water (100 mL) at room temperature. After extraction of the aqueous layer with $CHCl_3$ (2 × 100 mL), the combined organic extracts were dried over $MgSO_4$ and concentrated under vacuum before purification (the reaction with benzaldehyde or iodine at −70 °C required only 0.5 h, starting from 4-pyridinesulfonamide **2a**).

Diphenyl[2-(piperidinosulfonyl)-3-pyridyl]methanol (4a): from **1a** and benzophenone; recrystallized from Et_2O; yield 95%; mp 182 °C; ^1H NMR ($CDCl_3$), δ 6.75 (s, 1 H, OH), 7.25 (m, 12 H, $C_6H_5 + H_5 + H_4$), 8.55 (m, 1 H, H_6); IR 3360, 1600, 1570, 1550, 1490, 1465, 1450, 1440, 1430, 1375, 1160 cm^{-1}. Anal. Calcd for $C_{23}H_{24}N_2O_3S$: C, 67.62; H, 5.92; N, 6.86. Found: C, 67.4; H, 5.91; N, 6.78.

3-Deuterio-2-(piperidinosulfonyl)pyridine: from **1a** and CH_3OD. Recrystallization from Et_2O yields a mixture of **1a** (15%) and the 3-deuterio derivative (85%); mp 59 °C; ^1H NMR ($CDCl_3$) δ 7.55 (m, 1 H, H_5), 7.95 (m, 1.15 H, $H_3 + H_4$), 8.70 (dd, 1 H, H_6).

Phenyl[2-(piperidinosulfonyl)-3-pyridyl]methanol (9): from **1a** and benzaldehyde; recrystallized from Et_2O; yield 90%; mp 106 °C; ^1H NMR ($CDCl_3$) δ 3.85 (s, 1 H, OH), 6.75 (s, 1 H, CH), 7.35 (m, 6 H, $C_6H_5 + H_5$), 7.75 (dd, 1 H, H_4), 8.45 (dd, 1 H, H_6); IR 3490, 1605, 1580, 1565, 1500, 1470, 1450, 1420, 1435, 1335, 1170 cm^{-1}. Anal. Calcd for $C_{17}H_{20}N_2O_3S$: C, 61.42;, H, 6.06; N, 8.43. Found: C, 61.3; H, 6.06; N, 8.38.

3-Formyl-2-(piperidinosulfonyl)pyridine (12): from **1a** and dimethylformamide as for **19**; yield 55%; mp 79 °C; ^1H NMR ($CDCl_3$) δ 7.60 (dd, 1 H, H_5), 8.35 (d, 1 H, H_4), 8.75 (d, 1 H, H_6), 10.90 (s, 1 H, CHO); IR 1700, 1680, 1575, 1475, 1460, 1440, 1430, 1340, 1175 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2O_3S$: C, 51.93; H, 5.55; N, 11.02. Found: C, 51.8; H, 5.66; N, 10.5.

3-Iodo-2-(piperidinosulfonyl)pyridine (7): from **1a** and iodine; decolorized with $NaHSO_3$, decanted, extracted with $CHCl_3$, dried over $MgSO_4$, and concentrated under vacuum; yield 90%; mp 145 °C; ^1H NMR ($CDCl_3$) δ 7.10 (dd, 1 H, H_5), 8.35 (dd, 1 H, H_4), 8.50 (dd, 1 H, H_6); IR 1575, 1555, 1470, 1455, 1445, 1435, 1420, 1400, 1345, 1170 cm^{-1}. Anal. Calcd for $C_{10}H_{23}IN_2O_2S$: C, 34.10; H, 3.72; N, 7.95. Found: C, 33.5; H, 3.55; N, 7.38.

2-(Piperidinosulfonyl)pyridine-3-carboxylic Acid (13). Lithiated **1a** was quenched with dry ice (50 g). The product was hydrolyzed at 0 °C with H_2O (150 mL) and extracted with $CHCl_3$ (2 × 50 mL). The aqueous solution was acidified to pH 2 and extracted with $CHCl_3$ (2 × 50 mL). The organic extracts were dried ($MgSO_4$) and evaporated, and the residue was dried under vacuum: yield 85%; pasty melt at 150 °C; ^1H NMR ($CDCl_3$), δ 7.60 (dd, 1 H, H_5), 8.00 (dd, 1 H, H_4), 8.65 (dd, 1 H, H_6), 9.85 (s, 1 H, CO_2H); IR 3190, 1750, 1580, 1560, 1470, 1460, 1450, 1440, 1415 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2O_4S$: C, 48.88; H, 5.22; N, 10.36. Found: C, 48.5; H, 5.34; N, 10.2.

Diphenyl[4-(piperidinosulfonyl)-3-pyridyl]methanol (6a): from **2a** and benzophenone; purified by steam distillation and recrystallization from Et_2O; yield 95%; mp 135 °C; ^1H NMR ($CDCl_3$) δ 6.55 (s, 1 H, OH), 7.30 (s, 10 H, Ph), 7.65 (d, 1 H, H_5), 8.10 (s, 1 H, H_2), 8.65 (d, 1 H, H_6); IR 3480, 3420, 1600, 1585, 1565, 1535, 1495, 1465, 1450, 1400, 1335, 1170 cm^{-1}. Anal. Calcd for $C_{23}H_{24}N_2O_3S$: C, 67.62;, H, 5.92; N, 6.86. Found: C, 67.6; H, 6.06; N, 6.86.

3-Deuterio-4-(piperidinosulfonyl)pyridine: from **2a** and CH_3OD. Recrystallization from Et_2O yields quantitatively the 3-deuterio derivative; mp 122 °C; ^1H NMR ($CDCl_3$) δ 7.55 (d, 1.02 H, $H_5 + H_3$), 8.85 (m, 2 H, $H_2 + H_6$).

Phenyl[4-(piperidinosulfonyl)-3-pyridyl]methanol (16): from **2a** and benzaldehyde; purified by steam distillation, drying, and flash chromatography over silica gel (Et_2O); yield 88%; mp 79 °C; ^1H NMR (Me_2SO) δ 4.90 (s, 1 H, OH), 6.75 (s, 1 H, CH), 7.25 (s, 5 H, Ph), 7.60 (d, 1 H, H_5), 8.50 (d, 1 H, H_6), 8.80 (s, 1 H, H_2); IR 3500, 1570, 1500, 1460, 1455, 1450, 1420, 1335, 1170 cm^{-1}. Anal. Calcd for $C_{17}H_{20}N_2O_3S$: C, 61.42; H, 6.06; N, 8.43. Found: C, 61.2; H, 5.96; N, 8.22.

[5-(Hydroxyphenylmethyl)-4-(piperidinosulfonyl)-3-pyridyl]phenylmethanol (22): from **2a** and benzaldehyde; steam distillation, drying, and separation from **16** by flash chromatography over silica gel (Et_2O); yield 9%; mp 117 °C; ^1H NMR (Me_2SO) δ 4.50 (s, 1 H, OH), 6.75 (s, 1 H, CH), 7.25 (s, 5 H, Ph), 8.85 (s, 2 H, $H_2 + H_6$); IR 3500, 1600, 1580, 1495, 1470, 1450, 1440, 1420, 1340, 1160 cm^{-1}. Anal. Calcd for $C_{24}H_{26}N_2O_4S$: C, 65.71; H, 5.98; N, 6.39. Found: C, 65.8; H, 5.90; N, 6.27.

3-Iodo-4-(piperidinosulfonyl)pyridine (14): from **2a** and iodine as for **7**; separated from **21** by crystallization from Et_2O/hexane; yield 86%; mp 97 °C; ^1H NMR ($CDCl_3$) δ 7.95 (d, 1 H, H_5), 8.80 (d, 1 H, H_6), 9.25 (s, 1 H, H_2); IR 1555, 1465, 1455, 1445, 1335, 1170, 1060 cm^{-1}. Anal. Calcd for $C_{10}H_{13}IN_2O_2S$: C, 34.10; H, 3.72; N, 7.95. Found: C, 34.0; H, 3.78; N, 8.05.

3,5-Diiodo-4-(piperidinosulfonyl)pyridine (21): from **2a** and iodine; separated from **14** by crystallization from Et_2O/hexane; yield 7%; mp 133 °C; ^1H NMR ($CDCl_3$) δ 9.20 (s, 2 H, $H_2 + H_6$); IR 1620, 1550, 1480, 1460, 1440, 1420, 1340, 1180, 1150 cm^{-1}. Anal. Calcd for $C_{10}H_{12}I_2N_2O_2S$: C, 25.10; H, 2.53; N, 5.86. Found: C, 25.2; H, 2.54; N, 6.01.

3-Formyl-4-(piperidinosulfonyl)pyridine (19): from **2a** and dimethylformamide (2.5 equiv) at −40 °C for 1 h; decanted, extracted ($CHCl_3$), dried over $MgSO_4$, concentrated under vacuum, and recrystallized (Et_2O/hexane, 1/1); yield 90%; mp 90 °C; ^1H NMR ($CDCl_3$) δ 7.75 (d, 1 H, H_5), 9.05 (d, 1 H, H_6), 9.30 (s, 1 H, H_2), 11.20 (s, 1 H, CHO); IR 1690, 1560, 1465, 1445, 1045, 1340, 1180 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2O_3S$: C, 51.93; H, 5.55; N, 11.12. Found: C, 52.0; H, 5.52; N, 10.9.

4-(Piperidinosulfonyl)pyridine-3-carboxylic acid (20): from **1a** as for **13**; yield 75%; pasty melt at 140 °C; ^1H NMR (Me_2SO) δ 7.65 (d, 1 H, H_5), 8.70 (s, 1 H, H_2), 8.75 (d, 1 H, H_6); IR 3420, 1730, 1585, 1575, 1470, 1450, 1400 cm^{-1}. Anal. Calcd for $C_{11}H_{14}N_2O_4S$: C, 48.88; H, 5.22; N, 10.36. Found: C, 48.5; H, 5.34; N, 9.84.

2- and 4-[(Dialkylamino)sulfonyl]-3-pyridyl Ketones. Alcohols **9–11** and **16–18** (5 mmol) were oxidized with MnO_2 (50 mmol) in dry toluene (200 mL) at reflux in a Dean–Stark apparatus, with the reaction monitored by TLC on silica gel (Et_2O). The mixture was filtered on Celite, dried ($MgSO_4$), and evaporated under vacuum to give quantitative yields of ketones.

Phenyl[2-(piperidinosulfonyl)-3-pyridyl]methanone (23): from **9**, purified by flash chromatography over silica gel (Et_2O/hexane, 40/60); mp 104 °C; ^1H NMR ($CDCl_3$) δ 7.80 (m, 7 H, $H_4 + H_5 + C_6H_5$), 8.75 (dd, 1 H, H_6); IR 1680, 1600, 1585, 1555, 1470, 1455, 1405, 1345, 1175 cm^{-1}. Anal. Calcd for $C_{10}H_{18}N_2O_3S$: C, 61.80; H, 5.49; N, 8.48. Found: C, 61.9; H, 5.39; N, 8.46.

Phenyl[4-(piperidinosulfonyl)-3-pyridyl]methanone (26): from **16**, purified by crystallization from Et_2O; mp 90 °C; ^1H NMR ($CDCl_3$) δ 7.15 (m, 6 H, $H_5 + C_6H_5$), 8.55 (s, 1 H, H_2), 8.80 (d, 1 H, H_6); IR 1680, 1600, 1585, 1570, 1470, 1455, 1400, 1350, 1170 cm^{-1}. Anal. Calcd for $C_{17}H_{18}N_2O_3S$: C, 61.80; H, 5.49; N, 8.48. Found: C, 62.92; H, 5.34; N, 8.19.

(Piperidinosulfonyl)benzene (29).[9] Benzenesulfonyl chloride (10 g, 0.057 mol) was slowly added at room temperature to a

solution of piperidine (9.7 g, 0.114 mol) in dry toluene (50 mL). The mixture was stirred for 3 h and washed with water (3 × 50 mL). Drying over $MgSO_4$, evaporation of the solvent, and crystallization of the residue from Et_2O afforded **29** in 85% yield; mp 91 °C; ^1H NMR ($CDCl_3$) δ 7.55 (m, 5 H, C_6H_5); IR 1630, 1485, 1470, 1450, 1340, 1180 cm^{-1}. Anal. Calcd for $C_{11}H_{15}NO_2S$: C, 58.64; H, 6.71; N, 6.22. Found: C, 58.8; H, 6.85; N, 6.25.

Diphenyl[2-(piperidinosulfonyl)phenyl]methanol (30). Lithiation of **29** with LDA was carried out at 0 °C followed by reaction with benzophenone at −70 °C. Unreacted starting materials were removed by steam distillation. Flash chromatography of the dried product over silica gel (Et_2O/hexane, 15/75) yielded **30** (55%); mp 160 °C; ^1H NMR ($CDCl_3$) δ 6.85 (s, 1 H, OH), 7.25 (m, 12 H, $C_6H_5 + H_4 + H_5$), 7.90 (m, 1 H, H_3); IR 3370, 1595, 1580, 1540, 1490, 1445, 1430, 1405, 1330, 1145 cm^{-1}. Anal. Calcd for $C_{24}H_{25}NO_3S$: C, 70.71; H, 6.19; N, 3.44. Found: C, 70.7; H, 6.31; N, 3.36.

Registry No. **1a**, 106762-43-0; **1b**, 106762-44-1; **1c**, 106762-45-2; **2a**, 715-07-1; **2b**, 715-08-2; **2c**, 106762-42-9; **4a**, 106762-58-7; **4b**, 106762-59-8; **4c**, 106762-60-1; **5**, 33486-07-6; **6a**, 106762-46-3; **6b**, 106762-47-4; **6c**, 106762-48-5; **7**, 106762-66-7; **8**, 106762-61-2; **9**, 106762-62-3; **10**, 106762-63-4; **11**, 106762-64-5; **12**, 106762-65-6; **13**, 106762-67-8; **14**, 106762-51-0; **15**, 106762-53-2; **16**, 106762-49-6; **17**, 106762-54-3; **18**, 106762-55-4; **19**, 106762-56-5; **20**, 106762-57-6; **21**, 106762-52-1; **22**, 106762-50-9; **23**, 106762-69-0; **24**, 106762-70-3; **25**, 106762-68-9; **26**, 106762-72-5; **27**, 106762-73-6; **28**, 106762-71-4; **29**, 5033-23-8; **30**, 106762-74-7; $C_6H_5OC_6H_5$, 119-61-9; C_6H_5CHO, 100-52-7; I_2, 7553-56-2; $C_2H_5COC_2H_5$, 96-22-0; 2,4-$Cl_2C_6H_3CHO$, 874-42-0; H_3CCHO, 75-07-0; $(CH_3)_2NCHO$, 68-12-2; CO_2, 124-38-9; $C_6H_2SO_2Cl$, 98-09-9; piperidine, 110-89-4; morpholine, 110-91-8; pyrrolidine, 123-75-1; 4-(piperidinosulfonyl)pyridine oxide, 719-09-5; 4-(morpholinosulfonyl)pyridine oxide, 884-96-8; 4-(pyrrolidinosulfonyl)pyridine oxide, 106762-41-8; 2-pyridinethione, 2637-34-5.

Supplementary Material Available: Experimental procedures and complete ^1H NMR and IR spectral data for compounds 1, 2, 4, and **6**–**30** (16 pages). Ordering information is given on any current masthead page.

Notes

Iminium Ion Mediated Cyclizations of 4-Aryl-1,4-dihydropyridines. Regio- and Stereoselectivity in Intermolecular Reactions

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We have recently reported the generation of iminium ions from 4-aryl-1,4-dihydropyridines and the intramolecular trapping of these electrophilic intermediates with carbon–carbon double bonds[1] and reactive heterocycles.[2,3] We have also noted other cyclization modes for 1,4-dihydropyridines that either compete with iminium ion formation[4] or utilize the iminium species at a secondary stage in the cyclization.[5] We now report that the iminium ion derived from dimethyl 2,6-dimethyl-4-phenyl-1,4-dihydropyridine-3,5-dicarboxylate (**1**; Scheme I) can be generated under conditions of Lewis acid catalysis and efficiently trapped in an intermolecular sense by allyltrimethylsilane and styrene. The resulting products are formal $\pi_{4s} + \pi_{2s}$ cycloadducts derived from an inverse-electron-demand Diels–Alder reaction and are formed both regio- and stereoselectivity, reflecting endo addition of the dienophile to the electron-deficient iminium diene system.

Formal $\pi_{4s} + \pi_{2s}$ cycloaddition reactions between dienophiles and 2-aza dienes have been extensively studied.[6,7] This work has shown that both normal- and inverse-electron-demand Diels–Alder type reactions depend upon the electronic nature of substituents on the aza diene. In the case of inverse-electron-demand processes, the utilization of Lewis acid catalysis to render the diene more electron deficient has resulted in successful cyclization under mild conditions.[8-12]

Unlike the examples described above that relate to reaction of a 2-aza diene in which the nitrogen is either neutral or formally charged by virtue of complexation[11] with a Lewis acid, our published results[1-5] have described 2-aza diene systems that are positively charged from covalent binding of nitrogen to a proton or alkyl group. In this respect our work is perhaps more closely aligned mechanistically with that of Bradsher and co-workers,[13] who have demonstrated facile cationic polar cycloaddition between acridizinium salts and vinyl ethers, and that of Stevens et al.[14] and Franck et al.[15] It was therefore the

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