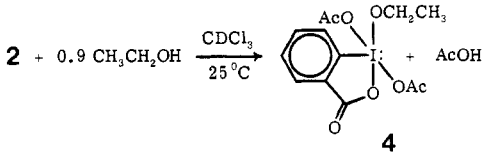
An alternative workup procedure[8] is useful for the synthesis of base-sensitive carbonyl compounds. Sodium thiosulfate reduces **3** to the water-soluble sodium salt of 2-iodobenzoic acid in sodium bicarbonate buffer in less than 10 min.

Either workup procedure is simpler and faster than that used for pyridinium chlorochromate,[3d] or other Cr(VI) reagents, which often produce tars which are purified with difficulty. Removal of the toxic and carcinogenic chromium species often requires time-consuming filtration procedures.[3c,d,g,h] The absence of such species in our procedure makes it particularly attractive for applications in medicinal chemistry. The use of dimethyl sulfoxide as an oxidizing agent[3f] also commonly requires much more complex workup procedures.

Recovery of the 2-iodo- or 2-iodosobenzoic acid for conversion to **2** simply involves acidification of the aqueous extracts and consistently results in a recovery greater than 95%.

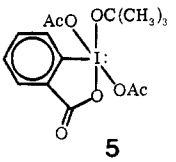
If 0.9 equiv of ethanol is added to a solution of **2** in chloroform-*d*, a compound is formed whose ^{1}H NMR is consistent with structure **4**. The methylene quartet ap-



4

pears at 4.68 ppm and the methyl triplet at 1.42 ppm. The quartet for the methylene group in uncomplexed ethanol, at 3.68 ppm, is not seen. Two singlets, at 2.03 and 2.10 ppm, correspond to the acetate attached to iodine and acetic acid, respectively. Periodinane **4** gives acetaldehyde and **3** over a period of 1.5 h at 25 °C.

If 1 equiv of *tert*-butyl alcohol is added to a solution of **2** in chloroform-*d*, a compound whose ^{1}H NMR is consistent with structure **5**, an analogue of **4**, is formed. This



5

compound is very stable in solution, but attempts to isolate it have not yet been successful. Both compounds **4** and **5** oxidize ethanol to acetaldehyde more rapidly than does **2**. If 1 equiv of ethanol is added to a solution of **4** or **5** at room temperature, its oxidation is almost instantaneous. The addition to **2** of as small an excess as 1.05 equiv, which would provide 0.05 equiv of alcohol beyond that required to form **4**, causes the reaction to go to completion in less than 20 min, much less time than is required for the oxidation of 0.9 equiv of ethanol. Addition of 1 equiv of a strong acid such as trifluoroacetic acid also catalyzes the reaction, giving almost instantaneous reaction. Added pyridine has little or no effect on the rate of the reaction. Further study of its mechanism is currently underway.

Periodinane **2** reacts much more rapidly with benzylic alcohols than with saturated alkanols. When 0.9 equiv of benzyl alcohol is added to a solution of **2** in chloroform-*d*, benzaldehyde is quantitatively formed in less than 20 min. A competitive oxidation using 1.00 equiv of **2** with 1.05 equiv each of ethanol and benzyl alcohol gives 78% benzaldehyde and 22% acetaldehyde. In similar competitive oxidations, periodinane **2** shows no selectivity between 2-propanol and ethanol. The basis for selectivity is not yet understood.

We have demonstrated that the readily accessible periodinane **2** is an effective reagent for the oxidation of alcohols to aldehydes or ketones with selectivity for benzyl alcohols. The reaction is catalyzed by acid or excess alcohol. The workup procedure is remarkably simple, and the conditions for reaction are very mild. By performing the reaction in the presence of pyridine and using the thiosulfate workup,[8] with sodium bicarbonate buffer, it is possible to maintain nearly neutral conditions throughout the entire reaction and isolation sequence.

Acknowledgment. This research was supported by a grant from the National Science Foundation (CHE 79-07-7905692). The NMR spectra were provided by the University of Illinois NSF Regional Instrumentation Facility (Grant CHE 79-16100) and mass spectra by facilities supported by grants from the National Institutes of Health (Grants CA 11388 and GM 16864).

Registry No. **1**, 61717-82-6; **2**, 87413-09-0; **3**, 1829-26-1; **4**, 87413-10-3; **5**, 87413-11-4; cyclohexanol, 108-93-0; *n*-octanol, 111-87-5; cyclooctanol, 696-71-9; benzyl alcohol, 100-51-6; 2,5-dimethoxybenzyl alcohol, 33524-31-1; 3,4,5-trimethoxybenzyl alcohol, 3840-31-1; cyclohexanone 2,4-dinitrophenylhydrazone, 1589-62-4; octanal 2,4-dinitrophenylhydrazone, 1726-77-8; cyclooctanone 2,4-dinitrophenylhydrazone, 1459-62-7; cyclooctanone, 502-49-8; benzaldehyde 2,4-dinitrophenylhydrazone, 1157-84-2; 2,5-dimethoxybenzaldehyde, 93-02-7; 3,4,5-trimethoxybenzaldehyde, 86-81-7; 2-iodobenzoic acid, 88-67-5; ethanol, 64-17-5; *tert*-butyl alcohol, 75-65-0.

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(8) The reaction mixture is diluted with ether and poured into saturated aqueous $NaHCO_3$ containing a sevenfold excess of $Na_2S_2O_3$. The mixture is stirred to dissolve the solid, and the layers are separated. The ether layer is extracted with saturated $NaHCO_3$ and with water. The ether is removed under vacuum and the product recrystallized or distilled.

Direct, Regiospecific 2-Lithiation of Pyridines and Pyridine 1-Oxides with in Situ Electrophilic Trapping

Summary: Efficient synthetic routes to 2-substituted pyridines and 2,6-disubstituted pyridine 1-oxides involving direct lithiation with the sterically hindered base lithium 2,2,6,6-tetramethylpiperidide (LiTMP) in the presence of electrophiles that are compatible with the base, e.g., trimethylsilyl chloride (Me_3SiCl) and hexafluoroacetone (HFA), are described.

Sir: The directed ortholithiation of benzenes with heteroatom-centered substituents, by reaction with alkyllithiums, is an important and well-known synthetic reaction.[1] In contrast, the directed 2-lithiation of pyridines has not been found to be practical because of the greater ease with which alkyllithium derivatives add to the pyridine ring rather than act as a base to deprotonate the pyridine ring.[2]

(1) For a recent review, see: Gschwend, H. W.; Rodriguez, H. R. *Org. React. (N.Y.)* **1979**, *26*, 1.
(2) (a) Wakefield, B. J. "The Chemistry of Organolithium Compounds"; Pergamon Press: Oxford, England, 1974; pp 112-116. (b) Francis, R. F.; Davis, W.; Wisener, J. T. *J. Org. Chem.* **1974**, *39*, 59.

0022-3263/83/1948-4156$01.50/0

Table I. Addition of Electrophiles to 3a at -107 °C

electrophile	yield[a] of 4a, % (E)
CH_3OD	83[b] (D)
$(CF_3)_2CO$	99[c] (-C(CF$_3$)$_2$OH)
$(Cl_2CBr)_2$	50 (Br)
I_2	58 (I)
PhCHO	60[b] (-CH(OH)Ph)

[a] Isolated yield. [b] Determined by ^{1}H NMR. [c] Formed upon warming the reaction mixture to -78 °C for 4 h without the further addition of HFA.

We report the efficient synthesis of 2-substituted pyridines and 2,6-disubstituted pyridine 1-oxides via regiospecific 2-lithiation with in situ trapping by electrophiles in a novel procedure.[3]

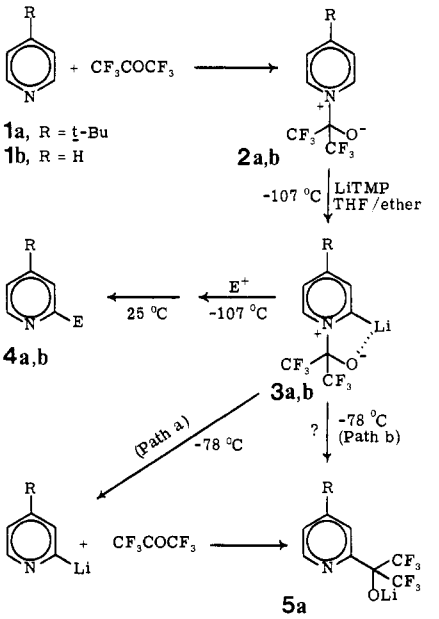
Although 2-lithiopyridines are available via low-temperature halogen–metal exchange,[4] the utility of this method is dependent on the accessibility of the halide precursor. Substituted 2-lithiopyridines have been recently prepared by ortholithiation of 3-halo[5] and 3-alkoxy pyridines[6] in rather specialized reactions utilizing the directive influence of the 3-substituents.

The acidifying inductive effect of the oxide substituent in pyridine 1-oxides, perhaps coupled with a lithium-chelating directive effect of the oxygen lone pairs, makes possible 2-lithiation or even 2,6-dilithiation of these compounds with alkyllithiums.[7] The yields of these reactions, however, are usually not high.[8]

Pyridines form weak complexes with fluoro ketones.[9] The formation of such a pyridinium complex is expected to result in increased acidity of the pyridine hydrogens, as is the case with pyridine 1-oxides. The complex also provides a chelating oxygen atom to direct a lithium base to the 2-position, in an interaction closely analogous to that responsible for the regiospecific 2-lithiation of benzylic alcohols.[10] We have found that HFA[11] complexes of pyridines (**2**)[12] and related compounds are regiospecifically lithiated with the relatively nonnucleophilic[13] LiTMP[14] at the 2-position. These aryllithium intermediates can subsequently be trapped in situ with HFA or with added electrophiles in a one-pot reaction.[16,17]

Table I lists the results of the addition of electrophiles

Scheme I

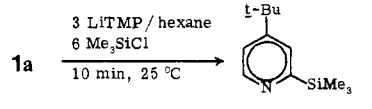


at −107 °C to **3a**, generated by the reaction of **2a** with LiTMP in THF/ether (90:10) at −107 °C for 1 h (Scheme I). Quenching **3b** with methanol-*d* gave 90% 2-deuteriopyridine. There is no evidence (^{1}H NMR) for incorporation of deuterium at the 4-position. Treatment of pyridine with LiTMP in the presence of tetramethylpiperidine-*d* at −78 °C for 20 min gave 28% deuterium incorporation at the 4-position and 48% of one deuterium in the 2- and 6-positions.[18] The much larger amount of 4-deuteration seen in the absence of HFA provides further evidence for the hypothesis that it is the complex of HFA with pyridine that is lithiated.

Evidence for the possible generality of this reaction is available in the observation that after 1 h at −107 °C with LiTMP, the HFA complex of quinoline reacts with added CH_3OD to give 23% deuterium incorporation, exclusively at the 2-position.

At −107 °C, complexes **2** and **3** are stable, giving no **5a** upon quenching at −107 °C. Conversion to **5a** does occur, however, upon warming to −78 °C for 4 h and then to room temperature. Such warming of dilute solutions (ca. 0.03 M) of **3a** produces **5a** in 35% yield, while very concentrated slurries of **3a** gave **5a** in greater than 99% yield. The addition of 0.5 equiv of HFA to the dilute solutions before warming increased the yield from 35% to 95%. This suggests that this is an intermolecular reaction of the 2-lithiopyridine (or perhaps of its complex with HFA at nitrogen) with uncomplexed HFA generated in situ by the dissociation of **3a** (path a), rather than an intramolecular migration of HFA (path b).

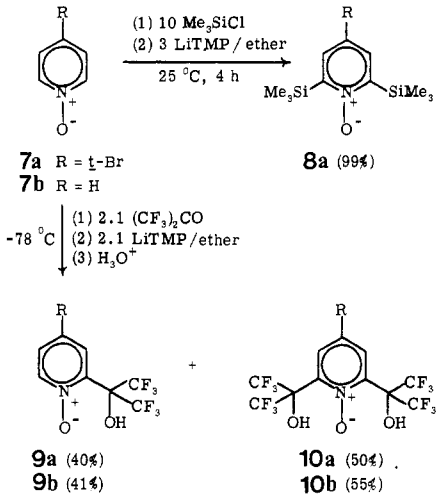
Pyridine **1a** is also directly lithiated at room temperature by LiTMP, in a reaction of considerable synthetic potential, if an electrophile compatible with the hindered base is present in situ to trap the aryllithium species before it decomposes or self-condenses. One suitable electrophile is Me_3SiCl.[19,20]



6

(3) Related observations have been reported: Krizan, T. D.; Martin, J. C. *J. Am. Chem. Soc.* **1983**, *105*, 6155.
(4) (a) Parham, W. E.; Piccirilli, R. M. *J. Org. Chem.* **1977**, *42*, 257. (b) Gilman, H.; Spatz, S. M. *J. Am. Chem. Soc.* **1940**, *62*, 446.
(5) Marsais, F.; Breant, P.; Ginguene, A.; Queguiner, G. *J. Organomet. Chem.* **1981**, *216*, 139.
(6) Marsais, F.; Le Nard, G.; Queguiner, G. *Synthesis* **1982**, 235.
(7) (a) Abramovitch, R. A.; Smith, E. M.; Knaus, E. E.; Saha, M. *J. Org. Chem.* **1972**, *37*, 1690. (b) Abramovitch, R. A.; Campbell, J.; Knaus, E. E.; Silhankova, A. *J. Heterocycl. Chem.* **1972**, *9*, 1367. (c) Abramovitch, R. A.; Coutts, R. T.; Smith, E. M. *J. Org. Chem.* **1972**, *37*, 3584.
(8) Trapping with various electrophiles gave 2,6-disubstituted pyridine 1-oxides in 3–48% yield.
(9) Schilling, M. L. M.; Roth, H. D. *J. Am. Chem. Soc.* **1980**, *102*, 4271.
(10) (a) Meyer, N.; Seebach, D. *Angew. Chem., Int. Ed. Engl.* **1978**, *17*, 521. (b) Perozzi, E. F.; Michalak, R. S.; Figuly, G. D.; Stevenson, W. H.; Dess, D. B.; Ross, M. R.; Martin, J. C. *J. Org. Chem.* **1981**, *46*, 1049.
(11) Stable pyridine complexes are also formed with carbonyl fluoride, sulfur dioxide, sulfur trioxide, and boron trifluoride, but attempts to lithiate these species have failed.
(12) Formation of **2a** at −78 °C is evidenced by a downfield shift of the pyridine hydrogens and by its precipitation from a THF solution upon addition of the HFA.
(13) Olofson, R. A.; Dougherty, C. M. *J. Am. Chem. Soc.* **1973**, *95*, 581.
(14) Lithium diisopropylamide gave much lower yields, possibly a result of reverse reaction of the aryllithium with diisopropylamine.[15] Potassium *tert*-butoxide gave no reaction.
(15) Marsais, F.; Laperdrix, B.; Güngör, T.; Mallet, M.; Queguiner, G. *J. Chem. Res., Miniprint* **1982**, 2863.
(16) Upon warming to room temperature, the HFA complex dissociates to give the free pyridine.
(17) All new compounds were characterized by nuclear magnetic resonance, mass spectra data, and elemental analyses.
(18) Reference 5 reports lithiation of 3-chloropyridine with lithium amides exclusively at the 4-position.

Scheme II



The ^{1}H NMR spectrum showed **6** to be the only aromatic compound present in the reaction mixture after 10 min.[21] If the deprotonation of **1a** occurs after its reaction with Me_3SiCl to give the *N*-(trimethylsilyl)pyridinium ion,[22] the equilibrium constant for the formation of such a reaction product is, in contrast to analogous reactions with HFA, too small to allow its detection by ^{1}H NMR. Only about 30% of the 2,6-disilylated product was formed after treatment with a 10-fold excess of LiTMP and a 30-fold excess of Me_3SiCl. This may reflect steric hindrance, by the 2-trimethylsilyl group, to activation of **6** by silylation at nitrogen, or it may reflect the inductive electron-releasing power of the 2-trimethylsilyl substituent. The above-mentioned H–D exchange seen for pyridine (a similar exchange is seen for **1a**)[22] in the presence of LiTMP shows that activation of pyridines by complexation with the electrophilic Me_3SiCl is not necessary for lithiation to occur. It is not yet clear whether such complexation may accelerate the lithiation in the presence of Me_3SiCl.

Although, as mentioned earlier, 2,6-disubstituted pyridine 1-oxides have been prepared via 2,6-dilithiopyridine 1-oxides with *n*-butyllithium as a lithiating agent, yields are low[7,8] (Scheme II). The direct lithiation of pyridine 1-oxides **7a** or **7b** with *n*-butyllithium at −78 °C, for example, gives **10a** (5%) or **10b** (20%). When the in situ trapping method is used, however, with lithiation by LiTMP in the presence of HFA, the yields of these two products rise to 50% and 55%, respectively, with the remainder of the pyridine 1-oxides being converted to the monosubstituted products **9a** and **9b**. The conversion of the monoalkylated pyridine **9a** to **10a** can be effected in 75% yield by using the same in situ lithiation procedures.

(19) Queguiner et al.[15] have very recently reported an in situ trapping using Me_3SiCl in the presence of lithium diisopropylamide in reaction with 2-bromopyridine. In their case the lithiation, leading to 2-bromo-3-(trimethylsilyl)pyridine, could reflect activation by the bromo substituent as well as the pyridine functionality.

(20) By ^{1}H or ^{13}C NMR, LiTMP appears to react rapidly at −78 °C with Me_3SiCl to give a complex. The rate of reaction of this basic species, or perhaps of the small amount of LiTMP in equilibrium with the complex to give lithiation of **1a** is fast enough to compete with decomposition of the complex to give tetramethylpiperidine.

(21) The addition of *n*-BuLi (in hexane) directly to tetramethylpiperidine at 0 °C gave, after 1 h at 25 °C, a slurry of LiTMP. First the Me_3SiCl and then pyridine **1a** was added to the slurry. In some cases the hexane was removed in vacuum and replaced by THF to give a concentrated homogeneous solution of LiTMP. The destruction of LiTMP in a 1 M solution in THF by reaction with solvent has a half-life of ca. 30 h at 25 °C.

(22) Addition of **1a** to LiTMP and *N*-deuteriotetramethylpiperidine in THF at −78 °C for 20 min gives 17% deuterium incorporation at the 2,6-positions in the pyridine.

The *N*-oxide products are deoxygenated, in high yield, by heating them with triphenylphosphine.

Complexation of Me_3SiCl or HFA to the oxygen of the 2-substituted derivatives of **7**, which is expected to be less hindered by a bulky 2-substituent than for complexation to the nitrogens of **5** and **6**, may facilitate the 6-lithiation.

The use of Me_3SiCl as the in situ trap, in a lithiation carried out in ether at 25 °C, results in 99% conversion of **7a** to **8a**. The trimethylsilyl groups introduced into the pyridine or pyridine 1-oxide nucleus by these in situ trapping procedures are easily replaced by ipso electrophilic substitution with a variety of electrophiles. This makes these methods adaptable to the synthesis of many substituted pyridines.

Acknowledgment. This research was supported in part by a grant from the National Science Foundation (NSF CHE 81-13142). The NMR spectra were provided by the University of Illinois Midwest NSF Regional NMR Facility (CHE 79-16100). Mass spectra were obtained from facilities provided under grants from the National Institutes of Health (CA 11388 and GM 16864).

Supplementary Material Available: Analytical and spectroscopic data for **4a**, **5a**, **6**, **8a**, **9**, and **10** plus the experimental procedure for the preparation of **5a** (3 pages). Ordering information is given on any current masthead page.

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Fluorodecarboxylation with Xenon Difluoride

Summary: The reaction between xenon difluoride and aliphatic carboxylic acids causes decarboxylation with replacement of the carboxyl group by fluorine.

Sir: Replacement of the carboxyl function with halogen (halodecarboxylation) in the Hunsdiecker and Kochi reactions comprises an extremely useful selective procedure for the synthesis of halogenated organic substances. However, halodecarboxylation is limited specifically in that the halogen cannot be fluorine.[1]

In our research on the selective introduction of fluorine into organic molecules[2a,g] we have discovered a novel fluorodecarboxylation method based on the reaction of carboxylic acids with xenon difluoride in the presence of hydrogen fluoride.[3] This reaction, shown in eq 1, is the

$$\mathrm{RCOOH} \xrightarrow[\mathrm{CH_2Cl_2,\ 20\ ^\circ C}]{\mathrm{XeF_2,HF}} \mathrm{RF} \qquad (1)$$

first report on the selective replacement of a carboxyl function with a fluorine atom. Yields of fluorinated products are good (54–84%), as shown in Table I.

(1) (a) Wilson, C. V. *Org. React.* **1957**, *9*, 332. (b) Kochi, J. K. *J. Am. Chem. Soc.* **1965**, *87*, 2500.

(2) (a) Patrick, T. B.; Scheibel, J. J.; Cantrell, G. L. *J. Org. Chem.* **1981**, *46*, 3917. (b) Patrick, T. B.; Scheibel, J. J.; Hall, W. E.; Lee, Y. H. *Ibid.* **1980**, *46*, 4492. (c) Patrick, T. B.; Cantrell, G. L.; Chang, C. Y. *J. Am. Chem. Soc.* **1979**, *101*, 7434. (d) Patrick, T. B.; Le Faivre, M. H.; Koertge, T. E. *J. Org. Chem.* **1974**, *39*, 1758. (e) Patrick, T. B.; Hayward, E. C. *Ibid.* **1974**, *39*, 2120. (f) Patrick, T. B.; Schield, J. A.; Kirchner, D. G. *Ibid.* **1974**, *39*, 1758. (g) Patrick, T. B.; Cantrell, G. L.; Inga, S. M. *Ibid.* **1980**, *45*, 1409.

(3) For a review on xenon difluoride in organic chemistry see: Filler, R. *Isr. J. Chem.* **1978**, *17*, 71.

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