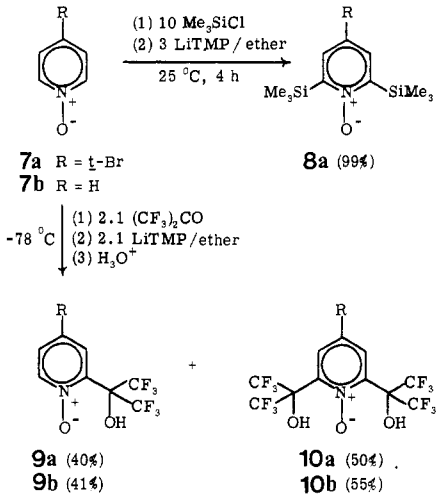
Scheme II



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.

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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.

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Table I. Yields and Properties of Fluorinated Compounds

acid	product[a]	% yield[b]	^{19}F NMR[c]	^{1}H NMR[d]	MS,[e] m/e
$PhCH_2COOH$	$PhCH_2F$	76	−207.0 (t, $^2J_{HF}$ = 48.4)	4.25 (d, CH_2), 7.15 (Ph)	110
$Ph(CH_2)_2COOH$	$PhCH_2CH_2F$	76	−215.3 (2 t, $^2J_{HF}$ = 47.0, $^3J_{HF}$ = 22.3)	2.8 (d, t), 4.4 (d, t), 7.13 (Ph)	124
$Ph(CH_2)_3COOH$	$PhCH_2CH_2CH_2F$*	60	−220.2 (2 t, $^2J_{HF}$ = 47.0, $^3J_{HF}$ = 25.0)	1-3 (CH_2, m), 7.13 (Ph)	138
Ph_3CCOOH	Ph_3CF	65	−126.1 (s)	7.21 (Ph)	262
$PhOCH_2COOH$	$PhOCH_2F$*	64	−148.7 (t, $^2J_{HF}$ = 53.7)	5.1 (d, CH_2), 7.15 (Ph)	126
2,4-Cl_2PhOCH_2COOH	2,4-Cl_2PhOCH_2F*	84	−149.8 (t, $^2J_{HF}$ = 53.7)	5.7 (d, CH_2), 7.15 (Ph)	195
$CH_3(CH_2)_{14}COOH$	$CH_3(CH_2)_{14}F$*	62	−218.3 (septet, $^2J_{HF}$ = 47.0, $^3J_{HF}$ = 24.0)	1.2-2[5] (m, CH_2), 5.5 (m, CH_2)	236
$CH_3(CH_2)_8COOH$	$CH_3(CH_2)_8F$*	54	−218.2 (septet, $^2J_{HF}$ = 46.4, $^3J_{HF}$ = 23.1)	1.6 (m), 5.5 (d, t, J = 50)	146
$PhCH(CH_2COOH)_2$	$PhCH(CH_2F)_2$*	60	−225.4 (d, t, $^2J_{HF}$ = 49.4, $^3J_{HF}$ = 20.8)	2.4-3 (m, CH_2), 6.9-7.4 (m, Ph)	156
$PhCH_2CH(CO_2H)_2$	$PhCH_2CHF_2$	68	−115.1 (t, d, $^2J_{HF}$ = 56.2, $^3J_{HF}$ = 17.1)	3.2 (CH_2, m), 5.5 (d), 7.2 (Ph)	142

[a] New compounds are marked with an asterisk and gave satisfactory C, H, and F analyses. Other compounds have been reported by: Weigert, F. J. *J. Org. Chem.* **1980**, *45*, 3476. [b] Isolated yields based on starting acid. [c] Chemical shifts are reported with respect to external $CFCl_3$ (ϕ 0.0 ppm). Multiplicates are given in parentheses along with coupling constants in hertz. [d] Shifts are reported relative to Me_4Si (δ 0.0). [e] 80 eV. Values are identical with calculated values.

Various primary, secondary, and tertiary aliphatic acids undergo successful fluorodecarboxylation. The structures may contain aryl, aryloxy, and ketonic functions without reaction difficulty; however, compounds containing hydroxyl groups, such as cholic acid, give complex mixtures. We have also noted that cyclohexanecarboxylic acid does not undergo fluorodecarboxylation successfully. Also, benzoic acid does not decarboxylate but instead gives benzoyl fluoride in low yield.[4]

The mechanism of the reaction is as yet unclear. Xenon difluoride is known to react with both aromatic rings and oxyacids. The reaction here is selective for the carboxyl function and thus suggests that the formation of a xenon ester is involved, $Xe(OCOR)_2$. DesMarteau has shown that xenon esters of oxyacids may be formed, but they have only limited stability with electronegative acids. Thus xenon trifluoroacetate fluoride, $XeF(OCOCF_3)$, decomposes above 20 °C to produce carbon dioxide and C_2F_6.[5]

Formation of the dimer, C_2F_6, indicates a radical breakdown of the ester and could indicate the manner in which our reaction proceeds as shown in eq 2.

$$RCOOH + XeF_2 \rightarrow (RCO_2)XeF \rightarrow RCO_2\cdot \rightarrow R\cdot \quad (2)$$

We have attempted unsuccessfully to trap the xenon ester from phenylacetic acid with triphenylethene, but we obtained only difluorotriphenylethane and benzyl fluoride. Furthermore, levulinic acid gave only 4-fluoro-2-butanone, and reaction at the ketone was not observed. Halo esters of levulinic acid are known to form cyclic lactones through reaction at the ketone carbonyl group.[6]

A typical procedure for fluorodecarboxylation with xenon difluoride is as follows. To a solution of hydrocinnamic acid (150 mg, 1 mmol) in 15 mL of methylene chloride contained in a polyethylene bottle is added xenon difluoride (170 mg, 1 mmol). Hydrogen fluoride is bubbled slowly into the solution for 60–100 s. The solution is stirred at 22 °C for 10–12 h. The resulting yellow mixture is washed with dilute sodium bicarbonate solution. The organic layer is dried and concentrated to yield pure 1-fluoro-2-phenylethane (76%).

Xenon difluoride offers a convenient method for the preparation of fluoroalkanes in a manner analogous to the Hunsdiecker reaction and thus is an attractive alternative to methods which require the use of SeF_4,[7] DAST,[8] or KF.[9] Our studies on the synthetic scope and mechanism of fluorodecarboxylation with xenon difluoride are continuing.

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