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2-FLUOROMETHYL-4,4,6-TRIMETHYL-1,3-OXAZINE AS A NEW REAGENT FOR THE PREPARATION OF α-FLUOROALDEHYDES

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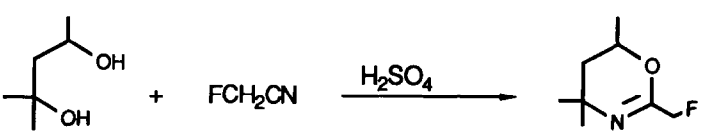
Summary. The title compound easily forms an anion on treatment with n-butyllithium. The anion reacts with electrophiles such as alkyl halides, aldehydes, and ketones. The resulting products furnish α-fluoroaldehydes after reduction and hydrolysis.

The substitution of a fluorine atom into an organic system often alters the properties of the system such that unique and valuable new substances are obtained. The wide range of important new fluorinated organic systems is very evident in medicinal and biological science[1-3].

The search for fluorinated reagents to serve as general intermediates in the synthesis of fluorinated materials is very active[4-6]. Although success has been achieved in the preparation of important α-fluoroacids and α-fluoroketones, the α-fluorinated aldehydes are an unknown class of compounds. In this communication, we describe the synthesis of α-fluoroaldehydes from a new fluorine-containing reagent, 2-fluoromethyl-4,4,6-trimethyl-1,3-oxazine (1), a modified Meyers' reagent with potential for general synthetic utility in the synthesis of fluorinated materials.

The oxazine (1) is prepared in 35% yield from fluoroacetonitrile and 2-methyl-1,3-pentanediol in sulfuric acid at -5 to 0°C, according to a modified procedure for the preparation of the non-fluorinated system described by Meyers et al[7,8].



1

The oxazine is metallated rapidly at -78°C by n-butyllithium, tert-butyllithium, or n-butyllithium-HMPA. The yellow anion is alkylated with electrophiles (alkyl halides, aldehydes, ketones) at -78°C as shown in Table I[9].

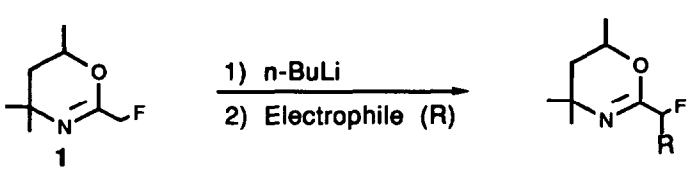


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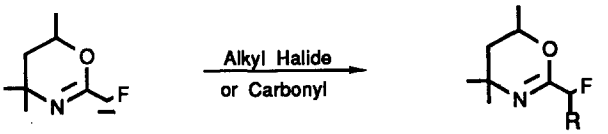
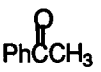
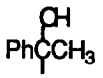
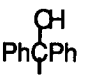
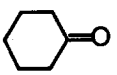
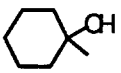
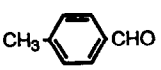
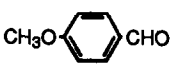
Table I



No	Alkyl halide	R	Yield %[a]	^{19}F NMR[b,c]
1	$PhCH_2Br$	$PhCH_2$	76	-109.4(m)
2	$PhCH_2Cl$	$PhCH_2$	30	-109.4(m)
3			66	-112.4(m)
4	CH_3I	CH_3	60	-105.3(m)
5	n-BuBr	n-Bu	58	-114.4(m)
	Carbonyl			
6			45	-121.8(d)
7			49	-118.5(d)
8			48	-128.0(d)
9			40	-122.7(m)
10			38	-122.8(m)

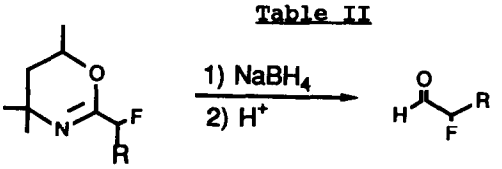
a) Yields of product isolated by flash chromatography.

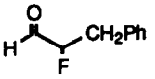
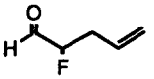
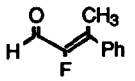
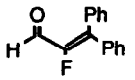
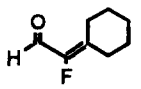
b) Chemical shifts in $CDCl_3$ relative to trifluoroacetic acid.

c) ^1H NMR and mass spectral data also agree with the assigned structure.

The α-alkylated oxazines are easily reduced with sodium borohydride and converted to the corresponding α-fluoroaldehydes on treatment with acid[7]. The compounds containing a β-hydroxyl group also undergo dehydration to yield the α, β-unsaturated α-fluoroaldehydes as shown in Table II[10].

Table II

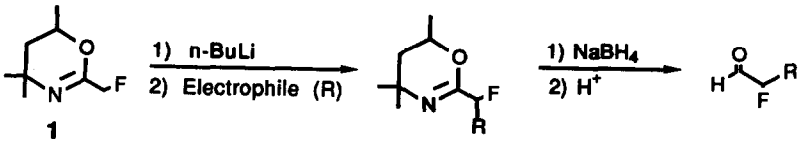


Reactant[a]	Product	% Yield	^{19}F NMR[b]
1		51%	-122.3(m)
3		59%	-123.9(m)
6		66%	-55.4(d)
7		70%	-54.4(d)
8		68%	-61.4(d)

a) Entry number from Table I.

b) Chemical shifts relative to trifluoroacetic acid in $CDCl_3$. ^{1}H NMR and mass spectral data were consistent with the assigned structures.

The overall process demonstrates the utility of **1** as a synthetic equivalent to fluoroacetaldehyde and is shown below. Further work on the synthetic utility of **1** is in progress.



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8. Fluoroacetonitrile (33 mmol, Aldrich Chemical Co.) was added to cold (0-3°C) concentrated H_2SO_4 followed by the addition of 2-methyl-2,4-pentanediol (30 mmol). The cold mixture was poured on ice, extracted with CH_2Cl_2 and neutralized with $NaHCO_3$ to pH 7 to give **1** as a yellow oil which gave 1.8 g (35%) of pure product after distillation at 28-30°C (1 mm). IR (neat) 1660 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ1.22 (s, CH_3) 1.28, 1.35 (d, CH_3), 1.75 (m, CH_2), 4.28 (m, CH), 4.45, 4.97 (d, CH_2F, J = 45.7 Hz), ^{19}F NMR ($CDCl_3$, TFA) δ-151 (t, FCH_2, J = 45.7 Hz). Anal. Calcd. for $C_8H_{14}NOF$: C, 60.38; H, 8.80; F, 11.95. Found: C, 60.33; H, 8.98; F, 11.90. Mass Spectrum (CI, Methane) Calcd M+1 160. Found 160.

9. Compound **1** (2 mmol) in dried THF is treated with 2.2 mmol of n-BuLi at -78°C during 2 min. The yellow-tan mixture is then treated with 2.0 mmol of alkyl halide or carbonyl electrophile.

10. The alkylated oxazine (Table I) (2 mmol) is reduced with 2 mmol of $NaBH_4$ at pH 6-8 at -35°C in 1:1 THF: 95% ETOH. The reduced product is treated with oxalic acid at reflux (1.5h) to give the aldehyde (Table II) after flash chromatography.

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