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Reaction of β-Fluorovinamidinium Salt with Grignard Reagents. Facile and Efficient Route to (Z)-α-Fluoro-α,β-unsaturated Aldehydes

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Abstract: β-Fluorovinamidinium salt (**1**) reacted cleanly with a variety of Grignard reagents in tetrahydrofuran at room temperature, followed by acid workup, to produce the corresponding (*Z*)-α-fluoro-α,β-unsaturated aldehydes (**3**) in good to excellent yields.

Keywords: Vinamidinium salts; Grignard reactions/reagents; Aldehydes; Fluorine and compounds

Vinamidinium (1,5-diazapentadienium) salts, vinylogs of amidinium compounds, have widely been utilized in organic synthesis since they have unique and versatile reactivities [1]. The salts are susceptible to substitution rather than addition reaction and react at their α and β carbon towards nucleophiles and electrophiles, respectively. Many types of vinamidinium salts appended with various substituents have hitherto been developed and used as potent three-carbon building blocks in organic synthesis [1-12]. Thus, the vinamidinium salts readily react with bifunctional hetero nucleophiles such as amidines, hydrazines and hydroxylamines to afford the corresponding heterocyclic compounds in good yields [2-5]. The salts also react with carbon nucleophiles such as enolate anions to produce dienaminones which could be useful intermediates in natural product synthesis [6,7]. In contrast to such extensive works, there are only a few reports on the fluorine-containing vinamidinium salts [13-15], which should be useful synthons for synthesizing fluorinated compounds of biological and material interest. In our continuing studies in this area, we have recently succeeded in preparing the salts having substituents such as fluorine [16], trifluoromethyl [17] or polyfluoroalkoxy [18] at the β carbon of the vinamidinium skeleton.

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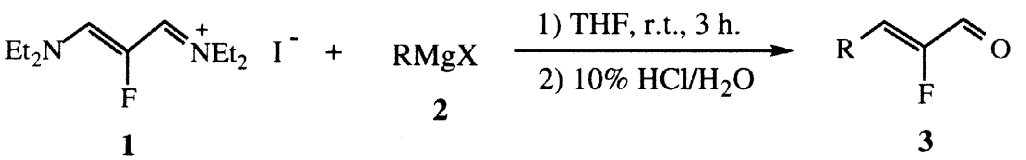
These salts have successfully been applied to synthesize fluorinated heterocycles [17,19,20], β-aminoacroleins [21], dienamino carbonyl compounds and aromatic compounds [22]. Then, a focus of our research interest has been addressed to studies for the scope and limitation of the synthetic utility of these fluorine-containing vinamidinium salts. Herein we wish to report the results of new reactions of β-fluorovinamidinium salt with Grignard reagents as carbon nucleophiles, providing a facile and efficient route to [*Z*]-α-fluoro-α,β-unsaturated aldehydes [23] which are useful intermediates for the synthesis of various organofluorine compounds.

The reaction of 1,5-diaza-1,1,5,5-tetraethyl-3-fluoro-1,3-pentadienium iodide (β-fluorovinamidinium salt) (**1**) with 1.1 equiv. of phenylmagnesium bromide (**2a**) in tetrahydrofuran (THF) at room temperature for 5 h, followed by treatment with 10% hydrochloric acid, gave α-fluorocinnamaldehyde (**3a**) [24] in 62% yield together with recovery of **1** (25%). However, when an excess amount (over 2.2 equiv.) of **2a** was employed, the reaction proceeded completely within 3 h to produce high yield (87%) of **3a** with no recovery of **1**. The aldehyde **3a** thus obtained was a single stereoisomer, which was determined to have the *Z* configuration based on the coupling constant (J = 34.3 Hz) between fluorine and vinylic hydrogen [25].

Scheme 1



The reactions with various Grignard reagents **2** (2.2 equiv.) were conducted under the same conditions as cited above (Scheme 1). Their results were summarized in the Table, together with ^{19}F NMR data for the respective products. Thus, all arylmagnesium bromides **2b-d** reacted cleanly to afford the corresponding α-fluoro-α,β-unsaturated aldehydes **3b-d** in high yields (85-87%) (Entries 2-4). Similarly, primary alkyl Grignard reagents **2e-g** also gave the aldehydes **3e-g** in moderate yields (Entries 5-7). Isopropylmagnesium bromide (**2h**) reacted smoothly to provide the aldehyde **3h** solely in a good NMR yield (Entry 8) whereas cyclohexyl-magnesium bromide (**2i**) produced an unidentified byproduct in addition to the aldehyde **3i** (Entry 9). The isolated yields of **3h** and **3i** were relatively lower than the NMR yields, primarily due to physical losses caused by the low boiling points of the respective aldehydes. The reaction with *t*-butylmagnesium chloride (**2j**) took place sluggishly to give the product **3j** in 47% NMR yield along with an unidentified product, the starting material **1** being left unchanged in 38% yield (Entry 10). Other Grignard reagents such as styryl-(**2k**), phenylethynyl-(**2l**) and 2-thienylmagensium bromides (**2m**) also nicely underwent the reaction to give the corresponding aldehydes **3k**, **3l** and **3m** in good yields (Entries 11-13). In all these reactions except **2l**, the aldehydes **3** thus obtained were only one stereoisomer

having the *Z* configuration. The Grignard reagent **2l** produced the aldehyde **3l** with two stereoisomers in a *Z/E* ratio of 93:7.

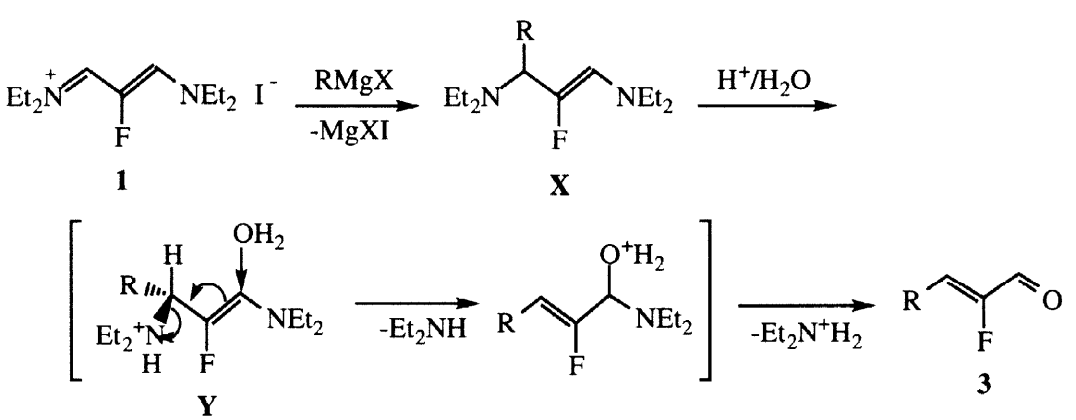
Table
Reaction of β-fluorovinamidinium salt **1** with Grignard reagents

Entry	Grignard reagent **2**	Product		^{19}F NMR[c]
		3	Yield/%[a]	δ ppm (*J*,Hz)
1	C_6H_5MgBr (**2a**)	**3a**	87 (94)	-129.06 (34.3, 17.1)
2	*p*-$CH_3OC_6H_4MgBr$ (**2b**)	**3b**	85	-132.19 (34.6, 17.4)
3	*p*-$CH_3C_6H_4MgBr$ (**2c**)	**3c**	86	-130.09 (34.3, 17.1)
4	α-$C_{10}H_7MgBr$ (**2d**)	**3d**	87	-129.15 (32.5, 16.5)
5	BuMgBr (**2e**)	**3e**	75 (90)	-134.38 (32.5, 18.3)
6	OctMgBr (**2f**)	**3f**	81	-134.36 (32.5, 18.3)
7	$C_6H_5CH_2MgCl$ (**2g**)	**3g**	57	-134.08 (31.6, 18.0)
8	*i*-PrMgBr (**2h**)	**3h**	50 (72)	-134.74 (31.9, 18.0)
9	*c*-HexMgBr (**2i**)	**3i**	43 (62)	-134.59 (33.1, 18.3)
10	*t*-BuMgCl (**2j**)	**3j**	-- (47)[b]	-132.17 (37.5, 17.6)
11	PhCH=CHMgBr (**2k**)	**3k**	76	-132.29 (30.1, 18.3)
12	PhC≡CMgBr (**2l**)	**3l**	78	(*Z*):-119.51 (28.6, 16.5)
				(*E*):-122.63 (10.5, 19.2)
13	 (**2m**)	**3m**	81	-128.24 (33.1, 17.7)

[a] Isolated yields. Values in parentheses are the yields determined by ^{19}F NMR.
[b] The salt **1** was recovered in 38%. [c] CCl_3F are used as internal standard and chemical shifts are negative for upfield shifts.

The following mechanism may be suggested for the formation of the aldehydes **3** (Scheme 2). The respective Grignard reagent attacks on the α carbon of **1** to form an enamine intermediate **X**. The intermediate undergoes acidic hydrolysis to produce the aldehyde **3**. The

Scheme 2



^{19}F NMR spectra of the reaction mixtures in all cases strongly suggested the existence of the intermediate, whose resonance appeared as doublet of doublets (J = 31-34 and 10-31 Hz) at around -70 ppm (upfield from external standard of CF3COOH). This peak shifted to around -57 ppm corresponding to the final product **3** after treatment with aqueous acid. Attempts to isolate this intermediate before acidic workup were in failure; it converted to **3** during column chromatography (silica gel or Aluminum oxide, activated, basic/hexane). The predominant formation of the *Z*-isomer may be explained by an S_N2' displacement of the ammonium group for the most stable comformer of a protonated species **Y**.

In summary, β-fluorovinamidinium salt **1** reacted cleanly with Grignard reagents to produce (*Z*)-α-fluoro-α,β-unsaturated aldehydes **3** in good yields. This reaction is general for aromatic, benzylic, aliphatic, vinylic and acetylenic Grignard reagents, and represents a facile and efficient route to the aldehydes. This reaction further substantiates the utility of this vinamidinium salt as a fluorinated three-carbon building block in organic synthesis.

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[24] (*Z*)-2-Fluoro-3-phenyl-2-propenal (**3a**): m.p. 46-47 °C. IR (KBr): 1688, 1634 cm^{-1}. ^1H NMR ($CDCl_3$, TMS): δ 6.63 (d, J=34.3 Hz, 1H), 7.42-7.51 (m, 5H), 9.35 (d, J=17.1 1H). ^{19}F NMR ($CDCl_3$, CCl_3F): δ -129.06 (dd, J= 34.3, 17.1 Hz). HRMS: Calcd for C_9H_7FO 150.0481, Found 150.0475.

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