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Reactions of β-Fluorovinamidinium Salt with Activated Methylene Compounds

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Abstract: β-Fluoro vinamidinium salt (**1**) reacted with 1.1 equiv. of methylene compounds activated with carbonyl or cyano groups in the presence of lithium diisopropylamide or sodium hydride and triethylamine in tetrahydrofuran at room temperature to give monofluorinated multifunctional dienaminones (**3**) and dienaminonitriles (**5**) in moderate to good yields. The reactions of **1** with 2.2 equiv. of enolates derived from β-keto esters at 80 °C gave the cyclization products, fluorinated isophthalates (**6**) in good yields, while a similar reaction with 2.2 equiv. of cyanoacetate and malononitrile produced the non-cyclic 1,3-dienecarbonitriles (**7**) in excellent yields.

Key words: Vinamidinium salt; Enolates; Fluorine and compounds; Dienamines; Cyano compounds; Enamino esters

Vinamidinium (1,5-diazapentadienium) salts are versatile compounds in organic synthesis. Since the salts have an alternation of electron density, the α-carbons are electron poor and are attacked by nucleophiles, and the β-carbon is electron rich and is attacked by electrophiles. The former type of reactions are of particular utility for the synthesis of some carbocyclic and heterocyclic compounds and the salts can serve as three-carbon building blocks in such reactions [1-8]. Although many types of vinamidinium salts have been developed and applied in organic synthetic chemistry, there are few reports dealing with fluorine-containing vinamidinium salts [9-11]. Recently, we have reported the preparation of β-fluoro [12-14], β-trifluoromethyl [15], and β-polyfluoroalkoxy vinamidinium salts [16] as well as their application to the synthesis of regiospecifically fluorinated heterocycles such as pyrimidines and pyrazoles. Herein we wish to report the results of the reactions of β-fluorovinamidinium salt **1** with carbon nucleophiles, anions derived from the methylene compounds activated with carbonyl or cyano groups [7,8], leading to monofluorinated multifunctional dienic and aromatic compounds.

On treating β-fluoro vinamidinium salt **1** [12] with the enolates generated from aceto-

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phenone (**2a**) (1.1 equiv.) with lithium diisopropylamide (LDA) (1.2 equiv.) in THF at room temperature for 1 h, 4-fluoro-1-phenyl-5-piperidino-2,4-pentadien-1-one (**3a**) was obtained in 55 % yield (Entry 1 in Table 1). The addition of triethylamine (3.0 equiv.) to the reaction mixture increased the yield of **3a** to 71% (Entry 2). Other enolates, such as those from 3-pentanone (**2b**), cyclopentanone (**2c**), γ-butyrolactone (**2d**), ethyl acetate (**2e**), and diethyl malonate (**2f**), also reacted with **1** under similar conditions to give the corresponding dienaminones **3b-d** or dienaminoates **3e,f** in moderate to good yields (Entries 3-7) (Scheme 1). However, methyl acetoacetate (**2g**) afforded only 13% yield of **3g**, a large amount (75 %) of starting salt **1** being recovered, even if the reaction was carried out for 24 h (Entry 8). Interestingly, when this reaction with **2g** was conducted at 80 °C for 3 h, the aromatic compound, dimethyl 5-fluoro-2-methylisophthalate (**6g**) was found to be produced as main product (Entry 9). Other methylene compounds activated with cyano group also participated nicely in the reaction with **1**. Thus, on treatment of malononitrile (**4a**) or ethyl cyanoacetate (**4b**) (1.1 equiv.) with **1** in the presence of NaH (1.2 equiv.) in THF at room temperature for 1 h, 3-fluoro-4-piperidino-1,3-butadiene-1,1-dicarbonitrile (**5a**) and ethyl 2-cyano-4-fluoro-5-piperidino-2,4-pentadienoate (**5b**) were given in 86 and 87% yields, respectively (Entries 10 and 11).

Scheme 1

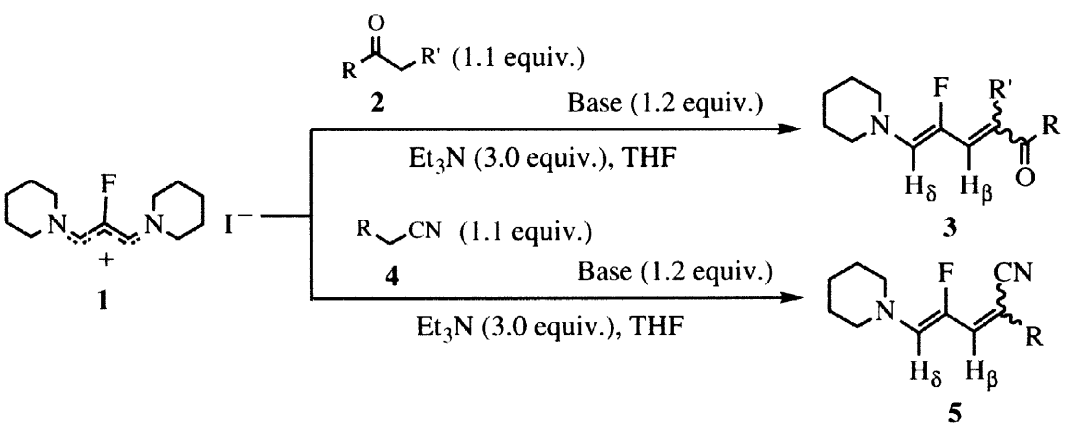


Table 1
Results of the reaction of **1** with 1.1 equiv. of methylene compounds **2** or **4**

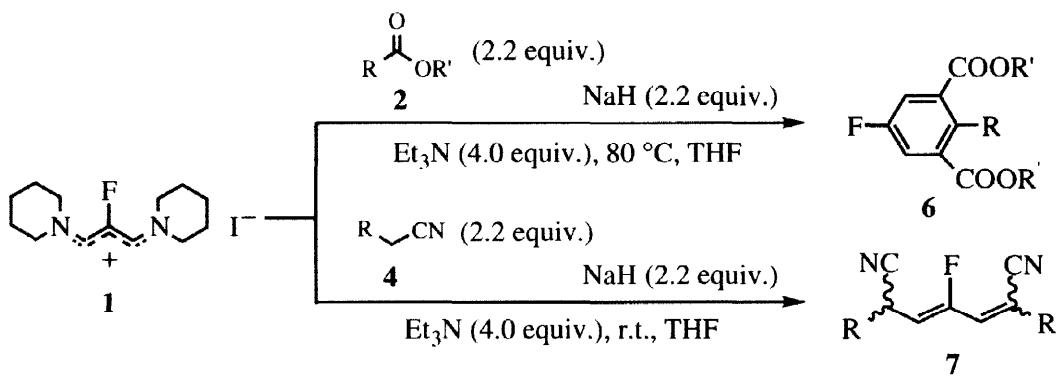
Entry	Methylene compound 2 or 4	Base	Additive	Temp (°C)	Time (h)	Product 3 or 5	Yield[a] (%)
1	Acetophenone (**2a**)	LDA	---	r.t.	1	**3a**	55
2	**2a**	LDA	Et_3N	r.t.	1	**3a**	71
3	3-Pentanone (**2b**)	LDA	Et_3N	80	3	**3b**	52
4	Cyclopentanone (**2c**)	LDA	Et_3N	r.t.	3	**3c**	47[b]
5	γ-Butyrolactone (**2d**)	LDA	Et_3N	r.t.	3	**3d**	46[b]
6	Ethyl acetate (**2e**)	LDA	Et_3N	r.t.	1	**3e**	80
7	Diethyl malonate (**2f**)	NaH	Et_3N	r.t.	1	**3f**	75
8	Methyl acetoacetate (**2g**)	NaH	Et_3N	r.t.	24	**3g**	13
9	**2g**	NaH	Et_3N	80	3	**3g**	8 (42)
10	Malononitrile (**4a**)	NaH	Et_3N	r.t.	1	**5a**	86
11	Ethyl cyanoacetate (**4b**)	NaH	Et_3N	r.t.	1	**5b**	87

[a] Isolated yields. Figures in parentheses are of the yield of aromatic compound **6**. [b] NMR yields.

The products **3** and **5** exhibited spectroscopic (IR, ^{1}H NMR, ^{19}F NMR, and HRMS) data which are fully consistent with the assigned structures.[1] All of the dienaminones and dienaminoates **3**, except **3g**, were a single geometric isomer. The structures of **3a** and **3e** were determined as the *E, Z* configuration on the basis of the coupling constants between Hα (=R') and Hβ ($J_{H\alpha H\beta}$=14.4-15.2 Hz) and between F and Hδ ($J_{FH\delta}$=28.6-29.2 Hz) [17]. The stereochemistry of **3b**, **3c**, and **3d** were also assigned as the *E, Z* configuration based on both the long range couplings between methyl or methylene protons of R' group and F, and H_β (^4J= ca. 2 Hz) [18] and on the coupling constant between F and Hδ ($J_{FH\delta}$=28.3-28.9 Hz). Although **3g** was a mixture of two stereoisomers in a ratio of 3:7 and **5b** was a single stereoisomer, their stereochemistry has not yet been determined.

The above-noted findings of the novel reaction with methyl acetoacetate (**2g**) leading to the aromatic compounds **6g** prompted us to further examine the reactions with a variety of β-keto esters. It was found that the use of over 2 equiv. of β-keto ester at high temperature was effective to obtain the corresponding isophthalates **6** in high yields (Scheme 2). Thus, the reaction of **1** with **2g** (2.2 equiv.) and sodium hydride (2.2 equiv.) in the presence of triethylamine (4.0 equiv.) in THF at 80 °C for 3 h gave isophthalate **6g**[2] in an 85 % yield. Similarly, other various β-keto esters **2h-m** afforded such satisfacory results as summarized in Table 2.

Scheme 2



In sharp contrast, the reactions with 2.2 equiv. of malononitrile (**4a**) and ethyl cyanoacetate (**4b**) at room temperature for 1 h provided disubstituted products, 3-fluoro-1,3-pentadiene-1,1,5,5-tetracarbonitrile (**7a**) and diethyl 4-fluoro-2,6-dicyano-2,4-heptadienedioate

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[1] For examples; **3a** Mp 84 °C; IR (KBr, cm^{-1}) 1695, 1660, 1640; ^{1}H NMR ($CDCl_3$, TMS, 500 MHz) δ 1.60 (br s, 6H), 3.39 (br s, 4H), 5.82 (d,*J*=28.6 Hz, 1H), 6.73 (d, *J*=14.4 Hz, 1H), 7.22 (dd, *J*=30.8, 14.4 Hz, 1H); 7.38-8.07 (m, 5H); ^{19}F NMR ($CDCl_3$, CCl_3F, 90 MHz) δ -150.65 (dd, *J*= 30.8, 28.6 Hz, 1F); HRMS: Calcd for $C_{16}H_{15}FNO$ 259.1393; Found 259.1367.
5b: Mp 98 °C; IR (KBr, cm^{-1}) 2190, 1675, 1635; ^{1}H NMR ($CDCl_3$, TMS, 500 MHz) δ 1.31 (t, *J*=7.1 Hz, 3H), 1.71 (br s, 6H), 3.60 (br s, 4H), 4.23 (q, *J*=7.1 Hz, 2H), 6.34 (d, *J*=25.9, 1H); 7.21 (d, *J*=31.3 Hz,1H); ^{19}F NMR ($CDCl_3$, CCl_3F, 90 MHz) δ -146.42 (dd, *J*= 25.9, 31.3 Hz, 1F); HRMS: Calcd for $C_{13}H_{17}FN_2O_2$ 252.1275; Found 252.1264.

[2] **6g**: Mp 53 °C; IR (KBr, cm^{-1}) 1735; ^{1}H NMR ($CDCl_3$, TMS, 500 MHz) δ 2.65 (s, 3H), 3.92 (s, 6H), 7.60 (d,*J*=8.6 Hz, 2H); ^{19}F NMR ($CDCl_3$, CCl_3F, 90 MHz) δ -116.82 (t, *J*= 8.6 Hz, 1F); HRMS: Calcd for $C_{11}H_{11}FO_4$ 226.0641; Found 226.0648.

Table 2
Results of the reactions of **1** with 2.2 equiv. of methylene compounds **2** or **4**

Entry	Metylene compound **2** or **4**	Temp. (°C)	Time (h)	Product **6** or **7**	Yield/%[a]
1	Methyl acetoacetate (**2g**)	80	3	**6g**	85
2	Methyl propionylacetate (**2h**)	80	3	**6h**	81
3	Ethyl butyrylacetate (**2i**)	80	3	**6i**	78
4	Ethyl isobutyrylacetate (**2j**)	80	24	**6j**	43
5	Methyl pentanoylacetate (**2k**)	80	3	**6k**	73
6	t-Butyl acetoacetate (**2l**)	80	5	**6l**	72
7	Ethyl benzoylacetate (**2m**)	80	24	**6m**	75
8	Malononitrile (**4a**)	r.t.	1	**7a**	94
9	Ethyl cyanoacetate (**4b**)	r.t.	1	**7b**	74

[a] Isolated yields.

(**7b**) in 94 and 74 % yields, respectively, without any cyclized products. Similarly, the reactions of **1** with 2.2 equiv. of acetophenone and of **3f** with 1.1 equiv. of **2f** at reflux temperature for 3 h produced the products corresponding to **7**, 4-fluoro-1,7-diphenyl-2,4-heptadiene-1,7-dione and diethyl 2,6-bis(ethoxycarbonyl)-4-fluoro-2,4-hexadienedioate in 57 and 79 % yields, respectively.

Further studies on the mechanism of the formation of the aromatic compounds **6**, as well as the synthetic applications of **1** are now in progress.

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