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Reactions of β-Fluorovinamidinium Salt with Bifunctional Hetero Nucleophiles. A New Synthetic Route to Fluorinated Heterocycles[1]

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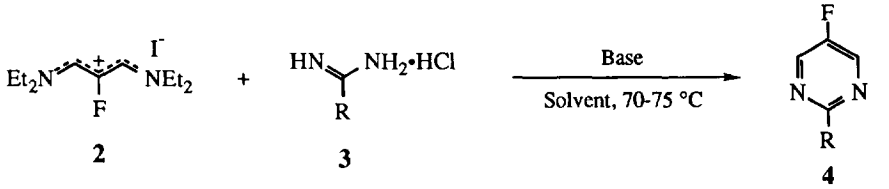
Abstract: β-Fluorovinamidinium salt (**2**), readily prepared from *N*-(2,3,3-trifluoro-1-propenyl)trimethylammonium iodide (**1**) and diethylamine, reacted with bifunctional hetero nucleophiles such as amidine and guanidine hydrochlorides in the presence of a base to afford regiospecifically monofluorinated pyrimidines **4** in good yields. The one-pot procedure starting from **1** was applicable for synthesizing heterocyclic compounds **4** in almost comparable yields.

Vinamidinium (1,5-diazapentadienium) salts, vinylogs of amidinium compounds, are the alkenes stabilized by "push-pull" effects between the electron-donating amino group and the electron-withdrawing ammonium group and thereby are susceptible to substitution rather than addition reactions. These salts are also characterized by their dual reactivities towards both nucleophiles and electrophiles on the α- and β-carbons, respectively. Such unique properties make these salts useful as a three-carbon synthon in organic synthesis and thus a number of investigations have hitherto been carried out on the preparation and reactions of various types of vinamidinium salts.[2] However, few or no reports dealing with fluorine-substituted vinamidinium salts have appeared in the literature.[3,4]

During the course of our studies on the synthetic application of polyfluoroalkyl-containing quaternary ammonium salts,[5] we recently succeeded in a very simple access to β-fluorovinamidinium salts that is based upon the reaction between *N*-(2,3,3-trifluoro-1-propenyl)trimethylammonium iodide (**1**)[5a] and primary or secondary amines.[6] These β-fluorovinamidinium salts should serve as a new building block for the synthesis of a variety of regiospecifically monofluorinated substances. In this communication we wish to disclose the preliminary results of the reactions of 1,1,5,5-tetraethyl-3-fluoro-1,5-diazapentadienium iodide (**2**)[6] with bifunctional nitrogen nucleophiles, which provide a novel and efficient method for synthesizing monofluorinated heterocyclic compounds in good yields.

The reactions of **2** with amidine (**3a-c**) and guanidine hydrochlorides (**3d,e**) were undertaken under various reaction conditions (Scheme 1). The results are summarized in Table 1. The treatment of **2** with benzamidine hydrochoride (**3a**) (1.5 equiv) in MeCN at 70-75 °C for 1 h resulted merely in a recovery of the starting salt (Entry 1). On adding a base to the reaction mixture, the expected reaction took place smoothly. Thus, the salt **2** was allowed to react with **3a** (1.5 equiv) in the presence of K_2CO_3 (1.5 equiv) at 70-75 °C for 1 h to give 5-fluoro-2-phenylpyrimidine (**4a**)[7] in 73% yield (Entry 2). Other bases than K_2CO_3, such as sodium methylate (MeONa) and diethylamine, were also effective for the reaction (Entries 3 and 4). Either protic or aprotic polar solvents like EtOH or MeCN, dimethyl sulfoxide (DMSO), and *N*,*N*-dimethylformamide (DMF) were equally employed to afford **4a** in high yields (Entries 4-7).[8]



a: R = Ph; **b**: R = Me; **c**: R = H; **d**: R = NH_2; **e**: R = NHMe

Scheme 1

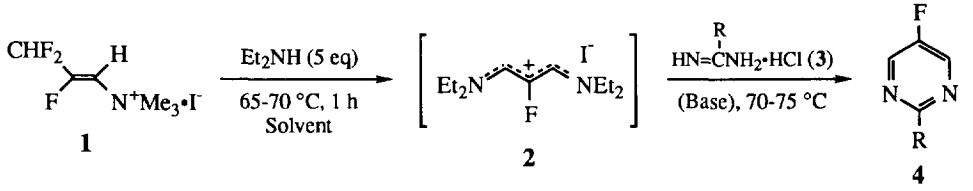
Table 1. Reaction of β-Fluorovinamidinium Salt (**2**) with Amidine and Guanidine Hydrochlorides (**3**)

Entry	R	**3** (equiv)	Base (equiv)	Solvent	Time/h	Yield[a]/% of **4**
1	Ph	**3a** (1.5)	—	MeCN	1	**4a** 0[b]
2	Ph	**3a** (1.5)	K_2CO_3 (1.5)	MeCN	1	**4a** 73
3	Ph	**3a** (1.5)	MeONa[c] (1.5)	MeCN	1	**4a** 90
4	Ph	**3a** (1.5)	Et_2NH (1.5)	MeCN	1	**4a** 85
5	Ph	**3a** (1.5)	Et_2NH (1.5)	EtOH	1	**4a** 84
6	Ph	**3a** (1.5)	Et_2NH (1.5)	DMSO	1	**4a** 84
7	Ph	**3a** (1.5)	Et_2NH (1.5)	DMF	1	**4a** 81
8	Me	**3b** (1.5)	Et_2NH (1.5)	MeCN	3	**4b** 73
9	Me	**3b** (1.5)	MeONa[c] (1.5)	MeCN	3	**4b** 76
10	Me	**3b** (3.0)	MeONa[c] (3.0)	MeCN	3	**4b** 82
11	H	**3c** (1.5)	Et_2NH (1.5)	MeCN	3	**4c** 55
12	H	**3c** (3.0)	Et_2NH (3.0)	MeCN	3	**4c** 75
13	H	**3c** (3.0)	MeONa[c] (3.0)	MeCN	3	**4c** 82
14	NH_2	**3d** (1.5)	Et_2NH (1.5)	MeCN	3	**4d** 23
15	NH_2	**3d** (3.0)	MeONa[c] (3.0)	MeCN	3	**4d** 53
16	NHMe	**3e** (1.5)	Et_2NH (1.5)	MeCN	3	**4e** 30
17	NHMe	**3e** (1.5)	MeONa[c] (1.5)	MeCN	3	**4e** 67
18	NHMe	**3e** (3.0)	MeONa[c] (3.0)	MeCN	3	**4e** 84

[a] Isolated yields. [b] The starting salt **2** was recovered unchanged. [c] A methanol solution (28 wt%) was used.

The similar reaction of **2** with acetamidine hydrochloride (**3b**) in MeCN at 70-75 °C for 3 h gave 5-fluoro-2-methylpyrimidine (**4b**)[7] in 73-76% yields (Entries 8 and 9), whereas the reaction with formamidine (**3c**), guanidine (**3d**), or 1-methylguanidine hydrochloride (**3e**) furnished low to fair yields of the corresponding 5-fluoropyrimidines **4c-e** (Entries 11, 14, 16, and 17). The latter unsatisfactory results were presumed in part to come from the thermal labilities of *in-situ* generated free amidine and guanidines. Three equivalents each of amidine **3b,c** or guanidine salt **3e** and base were used for the reaction, the yields of the products **4** being improved substantially (Entries 10, 12, 13, and 18). 2-Amino-5-fluoropyrimidine (**4d**)[7] was given in a no more than 53% yield even by using excess of **3d** (Entry 15).

The fact that diethylamine sufficiently acts as a base for effecting the above-described reaction of **2** with **3** prompted us to examine a one-pot procedure for the synthesis of heterocyclic compounds **4** (Scheme 2). Thus, *N*-(2,3,3-trifluoro-1-propenyl)trimethylammonium iodide (**1**) was treated with diethylamine (5.0 equiv) at 65-70 °C for 1 h to result in quantitative generation of **2**,[6] to which were successively added **3** (1.5 or 3.0 equiv) and, if necessary, a base (1.5 or 3.0 equiv) at room temperature. Then the mixture was stirred at 70-75 °C for 3-24 h. After the usual workup, the products **4** were isolated by distillation or column chromatography. The results of these one-pot reactions are summarized in Table 2.



Scheme 2

Table 2. Synthesis of 2-Substituted 5-Fluoropyrimidines (**4**) by One-pot Reaction

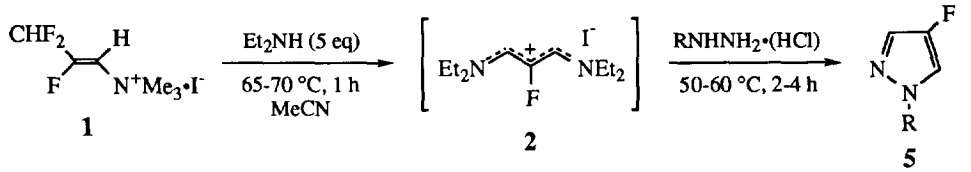
Entry	R	**3** (equiv)	Base (equiv)	Solvent	Time/h	Yield[a]/% of **4**
19	Ph	**3a** (1.5)	—	MeCN	3	**4a** 80
20	Ph	**3a** (3.0)	—	MeCN	3	**4a** 83
21	Ph	**3a** (1.5)	—	DMSO	3	**4a** 80
22	Ph	**3a** (1.5)	—	DMF	3	**4a** 79
23	Ph	**3a** (1.5)	—	EtOH	3	**4a** 69 [12][b]
24	Ph	**3a** (1.5)	Et_2NH (1.5)	MeCN	3	**4a** 81
25	Ph	**3a** (1.5)	MeONa[c] (1.5)	MeCN	3	**4a** 83
26	Me	**3b** (1.5)	—	MeCN	24	**4b** 53
27	Me	**3b** (3.0)	MeONa[c] (3.0)	MeCN	3	**4b** 76
28	H	**3c** (1.5)	—	MeCN	24	**4c** 40
29	H	**3c** (3.0)	—	MeCN	3	**4c** 62
30	H	**3c** (3.0)	Et_2NH (3.0)	MeCN	3	**4c** 67
31	NH_2	**3d** (3.0)	MeONa[c] (3.0)	MeCN	3	**4d** 48
32	NHMe	**3e** (3.0)	MeONa[c] (3.0)	MeCN	3	**4e** 75

[a] Isolated yields. [b] Yield of 5-ethoxy-2-phenylpyrimidine. [c] A methanol solution (28 wt%) was used.

The yields of the products **4** were nearly comparable with those (Table 1) obtained from the reaction using isolated vinamidinium salt **2**. To be noted is that the reaction in a protic solvent such as EtOH gave rise to 5-ethoxy-2-phenylpyrimidine[7] (12%) as by-product, together with **4a** (69%) (Entry 23). The former may not be produced *via* the reaction of **4a** with EtOH but through the reaction of **3a** with *N*-(2-ethoxy-3,3-difluoro-1-propenyl)trimethylammonium iodide[9] which is derived from **1** and EtOH.

It was found, moreover, that hydrazine derivatives participated nicely in the present one-pot reaction without a base. For instance, the treatment of *in-situ* generated **2** with hydrazine hydrochloride or methyl-

hydrazine (1.5 equiv) in MeCN at 50-60 °C for 2-4 h provided 4-fluoropyrazole (**5a**)[7] and 4-fluoro-1-methylpyrazole (**5b**)[7] in 57% and 90% yield, respectively, as shown below.



a: R = H; **b**: R = Me

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References and Notes

1. Presented at the 14th International Symposium on Fluorine Chemistry, Yokohama, Japan, August 1994, Abstr. No. 1P-45.
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7. All isolated products exhibited spectroscopic (IR, MS, ^{1}H NMR, and ^{19}F NMR) and analytical data which are fully consistent with the assigned structures.
8. The experimental procedure for Entry 3 is typical. To a stirred solution of **2** (0.984 g, 3 mmol) in MeCN (3 mL) was sequentially added benzamidine hydrochloride (**3a**) (0.705 g, 4.5 mmol) and a 28 wt% methanol solution of MeONa (0.868 g, 4.5 mmol) at room temperature and the mixture was heated at 70-75 °C for 1 h. After cooling to room temperature, the reaction mixture was poured into water (20 mL), extracted with CH_2Cl_2 (3 x 30 mL), and dried over Na_2SO_4. Evaporation of solvents and column chromatography on silica gel with hexane–EtOAc (5:1) gave analytically pure 5-fluoro-2-phenylpyrimidine (**4a**) (0.470 g): 90%; mp 66-67 °C (Lit.[4] mp 66.5-68.0 °C).
9. The preparation of *N*-(2-ethoxy-3,3-difluoro-1-propenyl)trimethylammonium iodide from **1** and its transformation to β-ethoxyvinamidinium salt have been carried out. Detailed results will be reported in due course.

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