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Efficient and General Synthesis of Novel β -Polyfluoroalkoxy Vinamidinium Salts

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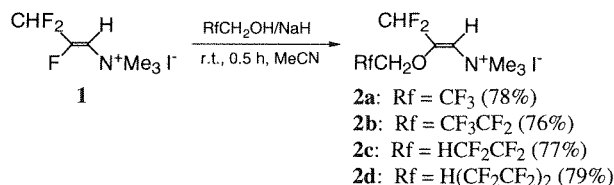
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Novel β -polyfluoroalkoxy vinamidinium salts **3** and/or **4** were synthesized in good yields by the reaction of *N*-(2-polyfluoroalkoxy-3,3-difluoro-1-propenyl)trimethylammonium iodides (**2**), prepared from *N*-(2,3,3-trifluoro-1-propenyl)trimethylammonium iodide (**1**), with secondary amines in MeCN at 70 °C for 1 h. The salts were also obtainable in comparable yields by the one-pot reaction of **1** with sodium polyfluoroalkoxide followed by treatment with amines.

Vinamidinium (1,5-diazapentadienium) salts, vinylogs of amidinium compounds, are regarded as 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. The salts are also characterized by their reactivities towards nucleophiles and electrophiles on the α - and β -carbons, respectively. These unique properties practically enable a wide range of their synthetic utility.¹ Although many types of salts carrying various substituents have been developed and used in organic synthesis,² there are few examples in the literature on the synthesis of fluorine-containing vinamidinium salts,³ which can serve as valuable intermediates for preparing fluorinated compounds of biological and material interest. Very recently we reported on the synthesis of β -monofluoro⁴ and β -trifluoromethyl⁵ vinamidinium salts and their applications to the preparation of fluorinated acroleins and heterocycles.^{5, 6}

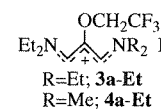
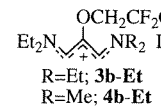
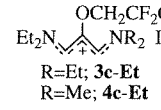
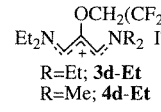
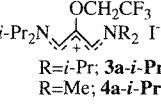

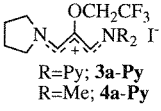

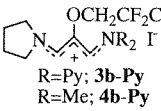

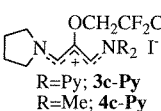

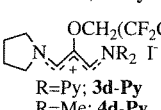

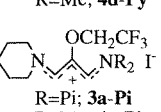

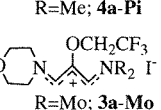
In our continuing studies on the synthesis and reactions of fluorinated vinamidinium salts, we have found that *N*-(2-polyfluoroalkoxy-3,3-difluoro-1-propenyl)trimethylammonium iodides (**2**) smoothly react with secondary amines under mild conditions to afford β -polyfluoroalkoxy vinamidinium salts **3** in good yields. Herein we wish to describe an efficient and general access to the synthesis of this novel type of vinamidinium salts, that can be a potent synthetic precursor of polyfluoroalkoxylated carbocycles and heterocycles difficult to prepare.

Polyfluoroalkoxy ammonium salts **2a-d**⁷ were prepared in 76-79% yields by the reactions of *N*-(2,3,3-trifluoro-1-propenyl)trimethylammonium iodide (**1**)⁸ with polyfluoroalcohols (1.1 equiv.) and NaH (1.1 equiv.) in MeCN at room temperature for 0.5 h.



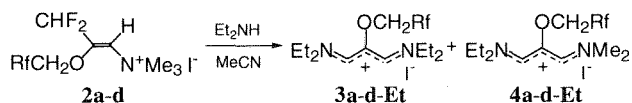
When **2a** was allowed to react with 5 equiv. of Et₂NH in the presence of molecular sieves 4A (MS4A) in MeCN at 70 °C for 1 h, a symmetrical vinamidinium salt, 1,1,5,5-tetraethyl-1,5-diaza-3-(2,2,2-trifluoroethoxy)pentadienium iodide (**3a-Et**)⁹ and

Table 1. Synthesis of β -Polyfluoroalkoxy Vinamidinium Salts

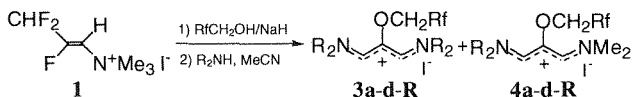
Entry	R ₂ NH	Product 3 and/or 4	Yield ^a /% of 3 and/or 4	Ratio ^b of 3 : 4
1	Et ₂ NH	 R=Et; 3a-Et R=Me; 4a-Et	70 (85)	72 : 28 (69 : 31)
2	Et ₂ NH	 R=Et; 3b-Et R=Me; 4b-Et	69 (81)	69 : 31 (70 : 30)
3	Et ₂ NH	 R=Et; 3c-Et R=Me; 4c-Et	74 (83)	70 : 30 (70 : 30)
4	Et ₂ NH	 R=Et; 3d-Et R=Me; 4d-Et	68 (85)	69 : 31 (69 : 31)
5	<i>i</i> -Pr ₂ NH	 R= <i>i</i> -Pr; 3a-i-Pr R=Me; 4a-i-Pr	82	0 : 100
6	 NH	 R=Py; 3a-Py R=Me; 4a-Py	74	100 : 0
7	 NH	 R=Py; 3b-Py R=Me; 4b-Py	68	100 : 0
8	 NH	 R=Py; 3c-Py R=Me; 4c-Py	79	100 : 0
9	 NH	 R=Py; 3d-Py R=Me; 4d-Py	72	100 : 0
10	 NH	 R=Pi; 3a-Pi R=Me; 4a-Pi	69	100 : 0
11	 NH	 R=Mo; 3a-Mo R=Me; 4a-Mo	67	100 : 0

^a Isolated yields. Figures in parentheses are of the yields based on **2** in the stepwise preparation. ^b Determined by ¹⁹F NMR. Figures in parentheses are of the ratios in the stepwise preparation.

an unsymmetrical salt, 1,1-diethyl-5,5-dimethyl-1,5-diaza-3-(2,2,2-trifluoroethoxy)pentadienium iodide (**4a-Et**)⁹ were obtained in 59% and 26% yields, respectively (Entry 1). Either elongation of the reaction time (10 h) or use of excess amine (10 equiv.) reduced the yield of the unsymmetrical salt to less than 5%. The absence of MS4A resulted in the formation of considerable amounts of β -(diethylamino)- and β -(dimethylamino)- α -(trifluoroethoxy)propenals,⁷ which may arise from the hydrolysis of *in-situ* formed vinamidinium salts.¹⁰ The reactions of other polyfluoroalkoxy ammonium salts **2b-d** with Et₂NH also took place nicely under similar conditions to afford the corresponding salts **3b-d-Et**⁷ and **4b-d-Et**⁷ (Entries 2-4). Interestingly, the yields and ratios of **3-Et** and **4-Et** were almost the same, irrespective of the length of polyfluoroalkyl group.



To simplify the procedure for the synthesis of the vinamidinium salts, we examined the one-pot reaction starting from *N*-(2,3,3-trifluoro-1-propenyl)trimethylammonium iodide (**1**). The ammonium iodide **1** was treated with trifluoroethanol (1.1 equiv.) and NaH (1.1 equiv.) in the presence of MS4A in MeCN at room temperature for 0.5 h. To this reaction mixture was successively added 5 equiv. of Et₂NH and then the mixture was stirred at 70 °C for 1 h. The usual workup followed by silica-gel column chromatography using AcOEt and EtOH provided the salts **3a-Et** and **4a-Et** in 70% combined yield (Entry 1). The yield was nearly comparable with overall yield (78% x 85% = 66%) given *via* the stepwise procedure using isolated **2**. Similarly, the reactions of **1** with other polyfluoroalcohols and secondary amines under the same conditions led to the corresponding symmetrical **3a-d-R** and/or unsymmetrical vinamidinium salts **4a-d-R** in good yields. The results of these one-pot syntheses starting from **1** are summarized in Table 1.



It should be noted that the ratio of **3** to **4** is strongly dependent on the secondary amine employed. Et₂NH afforded a mixture of **3a-d-Et** and **4a-d-Et** in a ratio of around 70 : 30 (Entries 1-4). Diisopropylamine, a bulky amine, gave only unsymmetrical salt **4a-i-Pr** (Entry 5). In contrast, cyclic amines such as pyrrolidine, piperidine, and morpholine yielded only symmetrical salts **3a-d-Py**, **3a-Pi**, and **3a-Mo**, respectively (Entries 6-11). The salt **4a-Et** was converted into the symmetrical salt **3a-Et** on treating with Et₂NH at 70 °C for 1 h in MeCN, whereas the treatment of **4a-i-Pr** with diisopropylamine

did not give any **3a-i-Pr**. These facts suggest that an N-N exchange process takes part in determining the ratio of **3** to **4**, where the bulkiness of the amine rather than its basicity or nucleophilicity plays a dominant role.

Further studies on the synthetic applications of **3** and **4**, including elucidation of their reactivities relative to β -fluoro and β -trifluoromethyl vinamidinium salts, are in progress.

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- 3a-Et**: Mp 103.5-104.7 °C; IR (KBr, cm⁻¹) 2978, 1654, 1597, 1443, 1315, 1265, 1061, 988; ¹H NMR (CDCl₃, TMS, 300 MHz) δ = 1.29 (t, *J* = 7.2 Hz, 6H), 1.40 (t, *J* = 7.2 Hz, 6H), 3.69 (q, *J* = 7.2 Hz, 8H), 4.04 (q, *J* = 8.2 Hz, 2H), 8.51 (s, 2H); ¹⁹F NMR (CDCl₃, CCl₃F, 90 MHz) δ = -73.75 (t, *J* = 8.2 Hz, 3F); SIMS 281 (M⁺-I), 689 (2M⁺-I). **4a-Et**: Mp 131.5-132.5 °C; IR (KBr, cm⁻¹) 2978, 1663, 1612, 1420, 1312, 1269, 1061, 964; ¹H NMR (CDCl₃, TMS, 300 MHz) δ = 1.30 (t, *J* = 7.2 Hz, 3H), 1.40 (t, *J* = 7.2 Hz, 3H), 3.48 (s, 1H), 3.48 (s, 1H), 3.65 (q, *J* = 7.2 Hz, 2H), 3.74 (q, *J* = 7.2 Hz, 2H), 4.22 (q, *J* = 8.3 Hz, 2H), 8.10 (s, 1H), 8.30 (s, 1H); ¹⁹F NMR (CDCl₃, CCl₃F, 90 MHz) δ = -73.42 (t, *J* = 8.3 Hz, 3F); SIMS 253 (M⁺-I), 633 (2M⁺-I).
- The propenals were obtained in 90% yield when the reaction was conducted in 20% aqueous MeCN.