Efficient and General Synthesis of Novel β-Polyfluoroalkoxy Vinamidinium Salts

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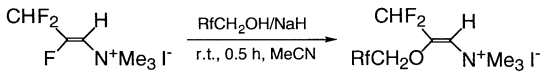
Novel β-polyfluoroalkoxy vinamidinium salts **3** and/or **4** were synthesized in good yields by the reaction of *N*-(2-polyfluoroalkoxy-3,3-difluoro-1-propenyl)trimethylammonium iodides (**2**), prepared from *N*-(2,3,3-trifluoro-1-propenyl)trimethylammonium iodide (**1**), with secondary amines in 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-monofluoro[4] and β-trifluoromethyl[5] 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.

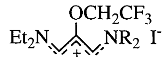
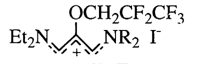
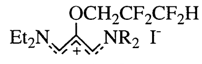
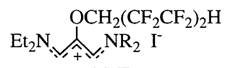
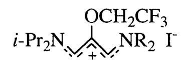
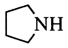
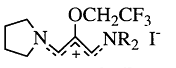
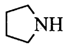
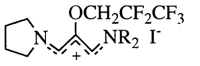
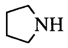
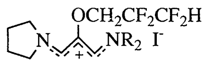
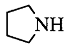
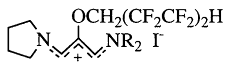
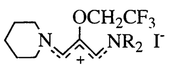
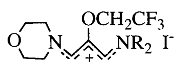


1

2a: Rf = CF_3 (78%)
2b: Rf = CF_3CF_2 (76%)
2c: Rf = HCF_2CF_2 (77%)
2d: Rf = $H(CF_2CF_2)_2$ (79%)

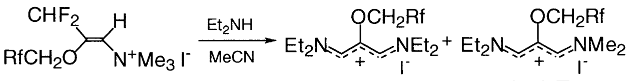
When **2a** was allowed to react with 5 equiv. of Et_2NH in the presence of molecular sieves 4A (MS4A) in MeCN at 70 °C for 1 h, a symmetrical vinamidinium salt, 1,1,5,5-tetraethyl-1,5-diaza-3-(2,2,2-trifluoroethoxy)pentadienium iodide (**3a-Et**)[9] and

Table 1. Synthesis of β-Polyfluoroalkoxy Vinamidinium Salts

Entry	R_2NH	Product **3** and/or **4**	Yield[a]/% of **3** and/or **4**	Ratio[b] of **3** : **4**
1	Et_2NH	 R=Et; **3a-Et** R=Me; **4a-Et**	70 (85)	72 : 28 (69 : 31)
2	Et_2NH	 R=Et; **3b-Et** R=Me; **4b-Et**	69 (81)	69 : 31 (70 : 30)
3	Et_2NH	 R=Et; **3c-Et** R=Me; **4c-Et**	74 (83)	70 : 30 (70 : 30)
4	Et_2NH	 R=Et; **3d-Et** R=Me; **4d-Et**	68 (85)	69 : 31 (69 : 31)
5	*i*-Pr_2NH	 R=*i*-Pr; **3a-*i*-Pr** R=Me; **4a-*i*-Pr**	82	0 : 100
6		 R=Py; **3a-Py** R=Me; **4a-Py**	74	100 : 0
7		 R=Py; **3b-Py** R=Me; **4b-Py**	68	100 : 0
8		 R=Py; **3c-Py** R=Me; **4c-Py**	79	100 : 0
9		 R=Py; **3d-Py** R=Me; **4d-Py**	72	100 : 0
10		 R=Pi; **3a-Pi** R=Me; **4a-Pi**	69	100 : 0
11		 R=Mo; **3a-Mo** R=Me; **4a-Mo**	67	100 : 0

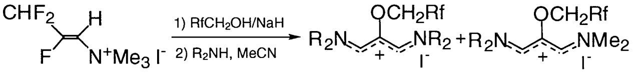
[a] Isolated yields. Figures in parentheses are of the yields based on **2** in the stepwise preparation. [b] Determined by ^{19}F NMR. Figures in parentheses are of the ratios in the stepwise preparation.

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 Et_2NH 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.



2a-d **3a-d-Et** **4a-d-Et**

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 Et_2NH 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.



1 **3a-d-R** **4a-d-R**

It should be noted that the ratio of **3** to **4** is strongly dependent on the secondary amine employed. Et_2NH 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 unsymmerical 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 Et_2NH 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.

References and Notes

1 For a review, see: D. Lloyd and H. McNab, *Angew. Chem. Int. Ed. Engl.*, **15**, 459 (1976). For recent works, see: J.T. Gupton, D.A. Krolikowski, R.H. Yu, S.W. Riesinger, and J.A. Sikorski, *J. Org. Chem.*, **55**, 4735 (1990); J.T. Gupton, D.A. Krolikowski, R.H. Yu, P. Vu, J.A. Sikorski, M.L. Dahl, and C.R. Jones, *J. Org. Chem..*, **57**, 5480 (1992); S.N. Balasubrahmanyam, B. Jeyashri, and I.N.N. Namboothiri, *Tetrahedron*, **50**, 8127 (1994); S.A. Petrich, F.A. Hicks, D.R. Wilkinson, J.G. Tarrant, S.M. Bruno, M. Vargas, K.N. Hosein, J.T. Gupton, and J.A. Sikorske, *Tetrahedron*, **51**, 1575 (1995).

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7 All isolated products gave satisfactory spectroscopic and analytical data.

8 The starting ammonium salt **1** was prepared from commercially available tetrafluoropropanol; H. Yamanaka, H. Ganbayashi, M. Kuwabara, K. Fukunishi, and M. Nomura, *Nippon Kagaku Kaishi*, **1988**, 1036; H. Yamanaka, S. Yamashita, K. Fukunishi, M. Kuwabara, T. Ishihara, and M. Nomura, *J. Fluorine Chem.*, **52**, 185 (1991).

9 **3a-Et**: Mp 103.5-104.7 °C; IR (KBr, cm^{-1}) 2978, 1654, 1597, 1443, 1315, 1265, 1061, 988; ^1H NMR ($CDCl_3$, TMS, 300 MHz) $\delta = 1.29$ (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); ^{19}F NMR ($CDCl_3$, CCl_3F, 90 MHz) $\delta = -73.75$ (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 ($CDCl_3$, TMS, 300 MHz) $\delta = 1.30$ (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); ^{19}F NMR ($CDCl_3$, CCl_3F, 90 MHz) $\delta = -73.42$ (t, $J = 8.3$ Hz, 3F); SIMS 253 (M^+-I), 633 ($2M^+$-I).

10 The propenals were obtained in 90% yield when the reaction was conducted in 20% aqueous MeCN.