

Synthesis of polyfluoroalkoxylated pyrimidines and pyrazoles by using novel β -polyfluoroalkoxy vinamidinium salts

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Abstract

Novel β -polyfluoroalkoxy vinamidinium salts **3** and/or **4** were prepared in good yields by the reaction of *N*-(2-polyfluoroalkoxy-3,3-difluoro-1-propenyl)trimethylammonium iodides (**2**) with secondary amines in acetonitrile at 70°C for 1 h. These vinamidinium salts readily reacted with bifunctional heteronucleophiles, such as amidines, guanidines and hydrazines, to give regiospecifically polyfluoroalkoxylated pyrimidines (**6**) and pyrazoles (**8**) in good yields. The one-pot procedure starting from *N*-(2,3,3-trifluoro-1-propenyl)trimethylammonium iodide (**1**), which was the precursor of **2**, was applicable for synthesizing the heterocyclic compounds in almost comparable yields with those obtained by the stepwise procedure using isolated **3** and **4**. © 1998 Elsevier Science S.A. All rights reserved.

Keywords: Fluoro vinamidinium salts; Building blocks; Synthesis of fluorinated heterocycles; Polyfluoroalkoxylated pyrimidines; Polyfluoroalkoxylated pyrazoles; N–N exchange reaction; *N*-(Polyfluoro-1-alkenyl)ammonium salts

1. Introduction

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 [1]. The salts are also characterized by their reactivity towards both nucleophiles and electrophiles on the α - and β -carbons, respectively. These unique properties practically enable a wide range of their synthetic utility [1–5]. Many types of salts modified with various substituents have hitherto been developed and used as potent three-carbon building blocks in organic synthesis [6–11], particularly in preparing heterocyclic and carbocyclic compounds. In contrast to such extensive works, there are only a few examples related to the preparation and reactions of fluorine-containing vinamidinium salts [12–14], which will serve as useful intermediates for synthesizing fluorinated compounds of biological and material interest. Very recently, we reported the preparation of β -monofluoro [15] and β -trifluoromethyl vinamidinium salts [16] and their applications to the synthe-

sis of fluorinated acroleins and heterocyclic compounds [16–18].

In our continuing studies to extend the chemistry of fluorinated vinamidinium salts, we have found that *N*-(2-polyfluoroalkoxy-3,3-difluoro-1-propenyl)trimethylammonium iodides (**2**) readily react with secondary amines under mild reaction conditions to give novel β -polyfluoroalkoxy vinamidinium salts **3** (and/or **4**) and that these vinamidinium salts can participate in the synthesis of a variety of regiospecifically polyfluoroalkoxylated compounds. In this paper we wish to describe the results of the preparation of these vinamidinium salts **3** (and/or **4**) and their reactions with bifunctional nitrogen nucleophiles, such as amidine, hydrazine and related compounds, giving rise to 5-polyfluoroalkoxy pyrimidine or 4-polyfluoroalkoxy pyrazole derivatives.

2. Results and discussion

2.1. Preparation of β -polyfluoroalkoxy vinamidinium salts

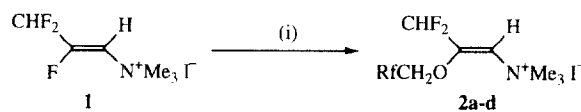
In our previous work [18] on the synthesis of monofluorinated heterocyclic compounds using *N*-(2,3,3-trifluoro-1-

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propenyl)trimethylammonium iodide (**1**)¹ [19,20], we had observed that the salt **1** underwent the facile replacement of the vinylic fluorine atom by ethoxy anion in ethanol under basic conditions to form *N*-(2-ethoxy-3,3-difluoro-1-propenyl)trimethylammonium iodide. We attempted to apply this reaction to prepare *N*-[(2-polyfluoroalkoxy)-3,3-difluoro-1-propenyl]trimethylammonium iodides (**2a–d**), which have a bright prospect of developing β -polyfluoroalkoxylated vinamidinium salts. Thus, the treatment of the ammonium iodide **1** with 1.1 equiv. each of polyfluoroalcohols and sodium hydride in acetonitrile (MeCN) at room temperature for 0.5 h was found to give the desired salts **2a–d** in 76–79% yields (Scheme 1). Employing excess amounts (over 2 equiv.) of polyfluoroalcohol and sodium hydride lowered the yields of **2**; both the vinylic fluorine and ammonium group were replaced with the polyfluoroalkoxy groups to afford 1,2-bis(polyfluoroalkoxy)-3,3-difluoro-1-propene.

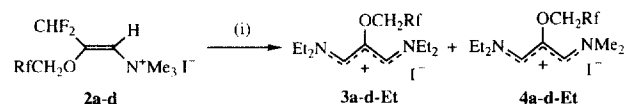
When *N*-[2-(2,2,2-trifluoroethoxy)-3,3-difluoro-1-propenyl]trimethylammonium iodide (**2a**) thus obtained was allowed to react with 5 equiv. of diethylamine (Et₂NH) in the presence of molecular sieves 4A (MS4A) in MeCN at 70°C for 1 h, a symmetrical vinamidinium salt, 1,1,5,5-tetraethyl-1,5-diaza-3-(2,2,2-trifluoroethoxy)pentadienium iodide (**3a-Et**) and an unsymmetrical vinamidinium salt, 1,1-diethyl-5,5-dimethyl-1,5-diaza-3-(2,2,2-trifluoroethoxy)pentadienium iodide (**4a-Et**) were obtained in 59 and 26% yields, respectively (Scheme 2 and Entry 1 in Table 1). Either elongation of the reaction time (10 h) or use of excess amine (10 equiv.) reduced the yield of the unsymmetrical salt **4a-Et** to the extent of less than 5%. The absence of MS4A resulted in the formation of considerable amounts of β -(diethylamino)- α -(trifluoroethoxy)propenal, Et₂NCH=C(OCH₂CF₃)-CHO, and β -(dimethylamino)- α -(trifluoroethoxy)propenal, Me₂NCH=C(OCH₂CF₃)-CHO, which may arise from the hydrolysis of the in situ-formed vinamidinium salts.² The reactions of other polyfluoroalkoxy ammonium salts **2b–d** with Et₂NH also proceeded nicely under similar conditions to provide the corresponding symmetrical salts **3b–d-Et** and unsymmetrical salts **4b–d-Et** (Entries 2–4). Interestingly, the yields and ratios of **3-Et** and **4-Et** were almost comparable, irrespective of the length of the polyfluoroalkyl groups.

In order to simplify the procedure for the synthesis of the vinamidinium salts, we explored the one-pot reaction using *N*-(2,3,3-trifluoro-1-propenyl)trimethylammonium iodide (**1**) as the starting material (Scheme 3). Thus, the ammonium iodide **1** was treated with 1.1 equiv. each of trifluoroethanol and sodium hydride in the presence of MS4A in MeCN at room temperature for 0.5 h. To this reaction mixture was added 5 equiv. of Et₂NH and then the whole mixture was heated at 70°C for 1 h. The usual workup followed by silica



a : Rf = CF₃, **b** : Rf = CF₃CF₂,
c : Rf = HCF₂CF₂, **d** : Rf = H(CF₂CF₂)₂

Scheme 1. Reagents and conditions: (i) RfCH₂OH, NaH, MeCN, room temperature, 0.5 h.



Scheme 2. Reagents and conditions: (i) Et₂NH, MeCN, MS4A, 70°C, 1 h.

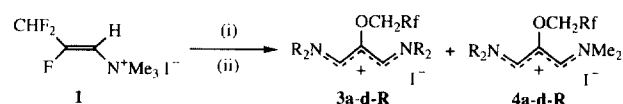
Table 1

Synthesis of β -polyfluoroalkoxy vinamidinium salts **3** (**4**) by one-pot (or stepwise) procedure

| Entry | R ₂ NH | Vinamidinium salt 3 and/or 4 | Yield ^a /% of 3 and 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-Pr R=Me; 4a-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 |

^aIsolated yields. Figures in parentheses are of the yields based on **2** in the stepwise reaction.

^bDetermined by ¹⁹F NMR. Figures in parentheses are of the ratios in the stepwise reaction.



Scheme 3. Reagents and conditions: (i) RfCH₂OH, NaH, MeCN, MS4A, room temperature, 0.5 h. (ii) R₂NH, MeCN, 70°C, 1 h.

¹ The starting ammonium salt **1** was easily prepared from commercially available tetrafluoropropanol.

² The propenals were obtained in around 90% yields when the reaction was conducted in 20% aqueous acetonitrile.

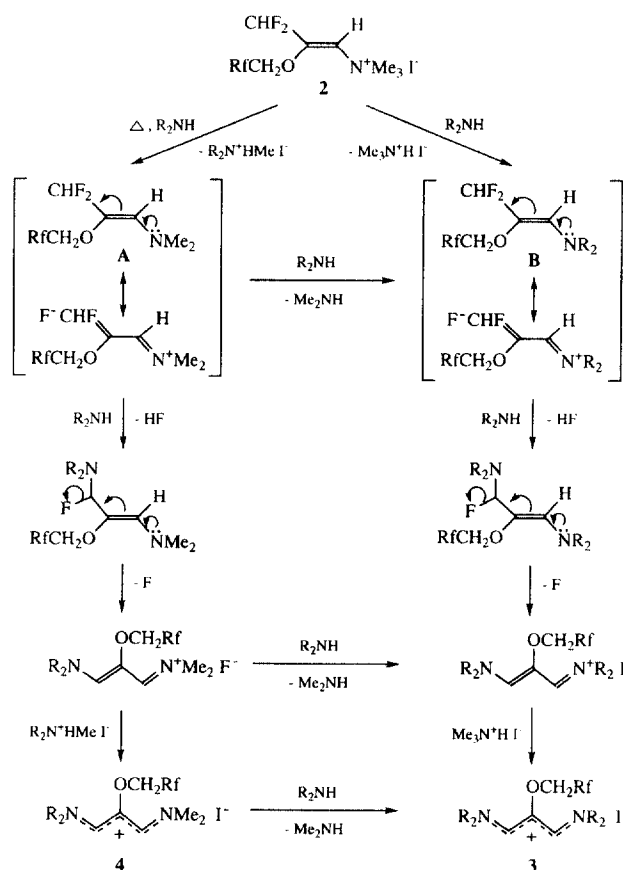
gel column chromatography using ethyl acetate and ethanol as eluents provided the salts **3a-Et** and **4a-Et** in 70% combined yield (Entry 1).

The yield of the salts was nearly identical with overall yield ($78\% \times 85\% = 66\%$) given via the stepwise procedure using isolated **2**. Similarly, the reactions of **1** with other polyfluoroalcohols and secondary amines (R_2NH) under the same reaction 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 preparations are summarized in Table 1.

It should be noted that the ratios of **3** to **4** are strongly dependent on the secondary amines employed. Et_2NH gave rise to a mixture of the symmetrical **3a-d-Et** and unsymmetrical salt **4a-d-Et** in a ratio of around 70:30 (Entries 1–4). Diisopropylamine, a bulky amine, yielded only the unsymmetrical salt **4-Prⁱ** (Entry 5). In contrast, cyclic amines, such as pyrrolidine, piperidine and morpholine, afforded only the symmetrical salt **3-Py**, **3-Pi** and **3-Mo**, respectively (Entries 6–11). The unsymmetrical salt **4a-Et** was converted into the symmetrical salt **3a-Et** on treating with an excess amount of Et_2NH at $70^\circ C$ for 3 h in MeCN, whereas the treatment of **4a-Prⁱ** with diisopropylamine under the same conditions did not give any **3a-Prⁱ**. These facts suggest that an amine–amine (N–N) exchange process takes part in determining the ratio of **3** to **4**, where the bulkiness rather than basicity or nucleophilicity of the amine plays a dominant role.

All vinamidinium salts obtained were pale yellow solids and hygroscopic. Once dried, these are stable indefinitely on storage and can be handled in air for short periods of time. The mass spectra (SIMS) of the salts did not exhibit the parent peak (M^+) but the parent minus iodide ($M - I^-$) and the cluster ion ($2M - I^-$) peaks, which are characteristic of an ammonium salt. Other spectroscopic (IR, 1H NMR, ^{19}F NMR and ^{13}C NMR) and analytical data of all isolated salts were fully consistent with the structure of the vinamidinium salt.

A possible mechanism for the formation of the vinamidinium salts **3** and **4** is shown in Scheme 4. The salt **2** may undergo a facile demethylation under reaction conditions cited above to form enamine **A**, which is transformed into another enamine **B** via the N–N exchange reaction between **A** and an added amine [21]. The enamine **B** could also be formed by the direct substitution of the ammonium group of **2** with the added amine except diisopropylamine. The resultant **B** will be subjected to an allylic substitution with the added amine to produce the symmetrical vinamidinium salt **3**. Concurrently, **3** may also be formed through the process that the enamine **A** undergoes the allylic substitution with the amine yielding the unsymmetrical vinamidinium salt **4**, followed by the N–N exchange reaction. Although neither enamines **A** nor **B** could be observed or isolated, trifluoromethylated enamines, which correspond to **A** and **B**, were isolated in good yields in the analogous reaction of *N*-(2,3,3,3-tetrafluoro-1-propenyl)trimethylammonium iodide with secondary amines [22].

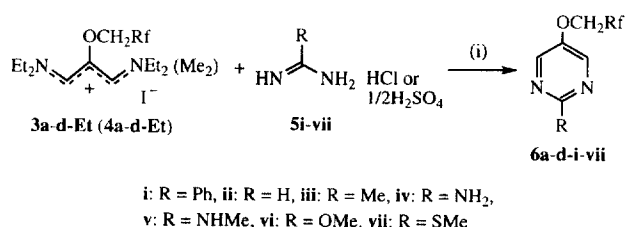


Scheme 4. A possible mechanism for the formation of the vinamidinium salts **3** and/or **4**.

2.2. Synthesis of polyfluoroalkoxylated heterocycles by the reaction of **3** (**4**) with bifunctional nitrogen nucleophiles

The reactions between the vinamidinium salts **3** (sole or mixture with **4**) and bifunctional nitrogen nucleophiles **5i–vii** were carried out under various conditions (Scheme 5). The results are summarized in Table 2.

The treatment of a mixture of **3a-Et** and **4a-Et** with benzamidine hydrochloride (**5i**) at room temperature for 3 h in MeCN did not afford any desired heterocyclic product, the starting salts being recovered unchanged. However, the addition of a base to the reaction mixture was found to allow the reaction to proceed smoothly. Thus, when a mixture of the salts **3a-Et** and **4a-Et** was allowed to react with **5i** (1.5 equiv.) in the presence of sodium methylate (1.5 equiv.) at room temperature for 3 h in MeCN, 2-methyl-5-(2,2,2-tri-



Scheme 5. Reagents and conditions: (i) MeONa, MeCN, MS4A, 3 h.

Table 2
Results of the reactions of vinamidinium salts **3** with amidines **5** or hydrazines **7**

| Entry | Vinamidinium salt 3a–d–R | 5 or 7 (equiv.) | NaOMe (equiv.) | Temperature (°C) | Yield of 6 or 8 (%) ^a |
|-------|---------------------------------|-------------------------------|----------------|------------------|--|
| 1 | 3a–Et ^b | 5i (1.5) | 1.5 | r.t. | 6a–i 90 |
| 2 | 3a–Et ^b | 5ii (1.5) | 1.5 | r.t. | 6a–ii 57 (79) |
| 3 | 3a–Et ^b | 5ii (1.5) | 1.5 | 70 | 6a–ii 66 (90) |
| 4 | 3a–Et ^b | 5iii (1.5) | 1.5 | r.t. | 6a–iii 70 |
| 5 | 3a–Et ^b | 5iii (1.5) | 1.5 | 70 | 6a–iii 80 (87) |
| 6 | 3a–Et ^b | 5iv (1.5) | 1.5 | 70 | 6a–iv 85 |
| 7 | 3a–Et ^b | 5v (1.5) | 1.5 | 70 | 6a–v 84 |
| 8 | 3a–Et ^b | 5vi (1.5) | 1.5 | 70 | 6a–vi 73 |
| 9 | 3a–Et ^b | 5vi (3.0) | 3.0 | 70 | 6a–vi 78 |
| 10 | 3a–Et ^b | 5vii (1.5) | 1.5 | 70 | 6a–vii 85 |
| 11 | 3b–Et ^b | 5i (1.5) | 1.5 | r.t. | 6b–i 87 |
| 12 | 3c–Et ^b | 5i (1.5) | 1.5 | r.t. | 6c–i 89 |
| 13 | 3d–Et ^b | 5i (1.5) | 1.5 | r.t. | 6d–i 88 |
| 14 | 3a–Py | 5i (1.5) | 1.5 | r.t. | 6a–i 61 |
| 15 | 3a–Mo | 5i (1.5) | 1.5 | r.t. | 6a–i 93 |
| 16 | 3a–Et ^b | 7i (1.5) | – | r.t. | 8a–i 17 |
| 17 | 3a–Et ^b | 7i (1.5) | – | 70 | 8a–i 44 |
| 18 | 3a–Et ^b | 7i (3.0) | – | 70 | 8a–i 50 |
| 19 | 3a–Et ^b | 7ii (1.5) | – | r.t. | 8a–ii 80 |
| 20 | 3a–Et ^b | 7iii (1.5) | – | r.t. | 8a–iii 85 (93) |
| 21 | 3c–Et ^b | 7iii (1.5) | – | r.t. | 8c–iii 89 |
| 22 | 3d–Et ^b | 7iii (1.5) | – | r.t. | 8d–iii 91 |

^aIsolated yields. Values in parentheses are of the yields determined by ¹⁹F NMR.

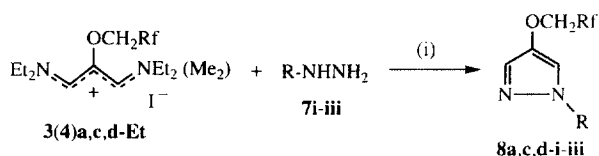
^bA mixture of **3–Et** and **4–Et** (ca. 70:30) was employed.

fluoroethoxy)pyrimidine (**6a–i**) was obtained in 90% yield (Entry 1). Similarly, on treating a mixture of **3a–Et** and **4a–Et** with formamide hydrochloride (**5ii**) or acetamide hydrochloride (**5iii**) at room temperature, the corresponding 5-(trifluoroethoxy)pyrimidines **6a–ii** and **6a–iii** were isolated in 57 and 66% yields, respectively (Entries 2 and 4). The reactions at 70°C led to the increase of the yields by around 10% in both cases (Entries 3 and 5). The reactions with other bifunctional nitrogen nucleophiles, such as guanidine hydrochloride (**5iv**), 1-methylguanidine hydrochloride (**5v**), 2-methylpseudourea sulfate (**5vi**) and 2-methyl-2-thiopseudourea sulfate (**5vii**), at 70°C for 3 h gave the corresponding 5-(trifluoroethoxy)pyrimidines **6a–iv–6a–vii** in good to excellent yields (Entries 6–10).

The length of the polyfluoroalkoxy group showed no effects on the reactivities of the vinamidinium salts; the salts **3b–d** carrying a longer polyfluoroalkoxy group reacted smoothly with **5i** at room temperature to give the corresponding 5-(polyfluoroalkoxy)pyrimidines **6b–i–6d–i** in good yields (87–89%), which were comparable with that (90%) obtained from **3a** having short trifluoroethoxy group (Entries

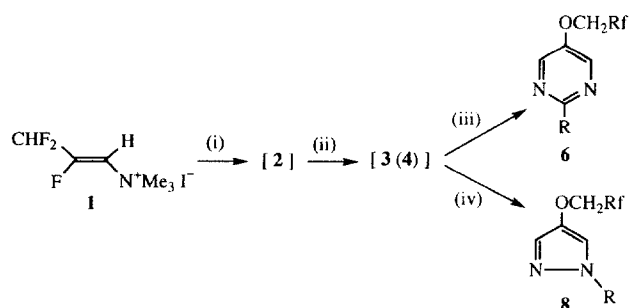
11–13 vs. 1). In contrast, the substituents on the nitrogens of the vinamidinium salt significantly affected the efficiency of the reaction. Thus, the salts **3a–Mo** gave the product **6a–i** in 93% yield (Entry 15), while **3a–Py** afforded **6a–i** in 61% yield (Entry 14) together with unreacted **3a–Py** (25% recovered) under the same conditions. These results seem to indicate that the reactivity of the vinamidinium salt towards amidine is related to the basicity of the amine generated by the N–N exchange with amidine [23].³

The hydrazines except phenylhydrazine also participated nicely in the present reaction (Scheme 6, Table 2). For example, the reaction of **3a** (**4a**)-**Et** with hydrazine (**7ii**) or methylhydrazine (**7iii**) at room temperature for 3 h in MeCN took place cleanly to produce 4-(2,2,2-trifluoroethoxy)pyrazole (**8a–ii**) or 1-methyl-4-(2,2,2-trifluoroethoxy)pyrazole (**8a–iii**) in 80 and 85% yield, respectively (Entries 19 and 20). Tetrafluoropropoxylated (**3c–Et**) and octafluoropentoxylated vinamidinium salts (**3d–Et**) also reacted smoothly with **7iii** at room temperature to give the corresponding pyrazoles **8c,d–iii** in excellent yields (Entries 21 and 22). However, the reaction of **3a** (**4a**)-**Et** with phenylhydrazine (**7i**) at room temperature gave only 17% yield of 1-phenyl-4-(2,2,2-trifluoroethoxy)pyrazole (**8a–i**), 77% of the starting salt being recovered unchanged (Entry 16). Even when the reaction temperature was raised up to 70°C and/or 3 equiv. of **7i** was used, the yield of **8a–i** was not more than 50% (Entries 17



Scheme 6. Reagents and conditions: (i) MeCN, MS4A, room temperature, or 70°C, 3 h.

³The pK_a values of the conjugate acids of morpholine and pyrrolidine are 8.33 and 11.13, respectively.

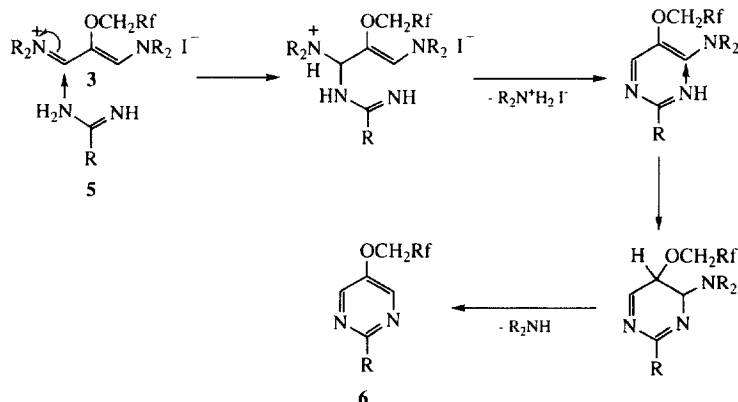


Scheme 7. Reagents and conditions: (i) RfCH_2OH (1.1 equiv.), NaH (1.1 equiv.), MeCN , MS4A , room temperature, 0.5 h. (ii) R_2NH (5.0 equiv.), 70°C , 1 h. (iii) Amidine hydrochloride (1.5 equiv.), NaOMe (1.5 equiv.), room temperature or 70°C , 3 h. (iv) Hydrazine (1.5 equiv.), room temperature, 3 h.

and 18). The low yield of **8a-i** may be ascribed to the low basicity (nucleophilicity) of the nitrogens of **7i**.






We also examined the one-pot procedure for the synthesis of heterocycles **6** and **8** starting from the ammonium salt **1** (Scheme 7). Thus, the ammonium iodide **1** was treated with polyfluoroalcohol (1.1 equiv.) and sodium hydride (1.1 equiv.) in the presence of MS4A in MeCN at room temperature for 0.5 h and then with 5 equiv. of secondary amine at 70°C for 1 h. To this reaction mixture were successively added 1.5 equiv. of amidine hydrochloride or hydrazine and 1.5 equiv. of sodium methylate. The whole mixture was stirred at 70°C for 3 h. After the usual workup, the desired products **6** and **8** were isolated by column chromatography. The results of these one-pot syntheses are summarized in Table 3. The yields of the products **6** and **8** were nearly comparable with those (Table 2) obtained from the reaction using isolated vinamidinium salts **3** and/or **4**.

A possible mechanism for the formation of the heterocycles **6** is shown in Scheme 8. Free amino group of the amidine formed in situ from the amidinium salt may initially attack to the α -carbon of the vinamidinium salt to remove dialkylamine through the N–N exchange reaction. The resulting imine intermediate will subsequently cyclize intramolecularly to yield dihydropyrimidine, followed by a loss of another



Scheme 8. A possible mechanism for the formation of the pyrimidines **6**.

Table 3
Synthesis of pyrimidines **6** or pyrazoles **8** by one-pot procedure

| Entry | RfCH_2OH | Secondary amine | Amidine 5 or hydrazine 7 | Yield/% of 6 or 8 | |
|-------|---|---|--|---------------------------------|----|
| 1 | $\text{CF}_3\text{CH}_2\text{OH}$ (a) | Et_2NH | 5i | 6a-i | 86 |
| 2 | $\text{CF}_3\text{CH}_2\text{OH}$ (a) | Et_2NH | 5iii | 6a-iii | 89 |
| 3 | $\text{CF}_3\text{CH}_2\text{OH}$ (a) | Et_2NH | 5v | 6a-v | 88 |
| 4 | $\text{CF}_3\text{CH}_2\text{OH}$ (a) | Et_2NH | 5vi | 6a-vi | 81 |
| 5 | $\text{CF}_3\text{CH}_2\text{OH}$ (a) | <i>i</i> - Pr_2NH | 5i | 6a-i | 72 |
| 6 | $\text{CF}_3\text{CH}_2\text{OH}$ (a) |  | 5i | 6a-i | 61 |
| 7 | $\text{CF}_3\text{CH}_2\text{OH}$ (a) |  | 5iv | 6a-iv | 66 |
| 8 | $\text{CF}_3\text{CH}_2\text{OH}$ (a) |  | 5i | 6a-i | 75 |
| 9 | $\text{CF}_3\text{CH}_2\text{OH}$ (a) |  | 5i | 6a-i | 71 |
| 10 | $\text{CF}_3\text{CH}_2\text{OH}$ (a) |  | 5vii | 6a-vii | 62 |
| 11 | $\text{CF}_3\text{CF}_2\text{CH}_2\text{OH}$ (b) | Et_2NH | 5i | 6b-i | 79 |
| 12 | $\text{H}(\text{CF}_2)_4\text{CH}_2\text{OH}$ (d) | Et_2NH | 5i | 6d-i | 90 |
| 13 | $\text{CF}_3\text{CH}_2\text{OH}$ (a) | Et_2NH | 7iii | 8a-iii | 72 |
| 14 | $\text{HCF}_2\text{CF}_2\text{CH}_2\text{OH}$ (c) | Et_2NH | 7iii | 8c-iii | 68 |

dialkylamine to give the final product **6**. Attempts to observe or isolate the proposed intermediates were not successful.

Pyrazoles **8** should also be formed via a similar mechanism.

3. Experimental details

3.1. Measurements and materials

Infrared spectra (IR) were measured in a liquid film or KBr disk method with a Shimadzu FTIR-8200PC spectrophotometer. ^1H and ^{13}C NMR spectra were obtained with a GE QE-300 (300 MHz for ^1H and 75 MHz for ^{13}C) spectrometer in a chloroform-*d* (CDCl_3) or dimethyl sulfoxide-*d*₆ ($\text{DMSO-}d_6$) solution with tetramethylsilane as an internal reference. A JEOL JNM EX90 (84.10 MHz) and a Hitachi R-24F (56.47 MHz) spectrometer were used to measure ^{19}F NMR spectra in CDCl_3 or $\text{DMSO-}d_6$ with trichlorofluoromethane as an internal standard. High resolution mass spec-

tra (HRMS) were taken on a Hitachi M-80B mass spectrometer operating at an ionization potential of 70 eV. Mass spectra for the ammonium and vinamidinium salts were measured by secondary ion mass spectra method (SIMS). Melting points were obtained on a Shimadzu MM-2 micro melting point determination apparatus and are uncorrected. The elemental analyses of products gave satisfactory results.

N-[2-(2,3,3-Trifluoro-1-propenyl)trimethylammonium iodide (**1**)¹ was prepared according to the method reported recently by Yamanaka et al. [19,20]. All chemicals are of reagent grade and, if necessary, were purified in a conventional manner before use. Acetonitrile (MeCN) was distilled from calcium hydride and stored under argon.

All reactions were carried out under an atmosphere of argon.

3.2. Preparation of vinamidinium salts **3** and/or **4**

3.2.1. Preparation of *N*-[2-(polyfluoroalkoxy)-3,3-difluoro-1-propenyl]trimethylammonium iodides (**2a–d**)

To a solution of the ammonium iodide **1** (5.621 g, 20.0 mmol) and 2,2,2-trifluoroethanol (2.201 g, 22.0 mmol) in MeCN (30 ml) was gradually added sodium hydride (0.528 g, 22.0 mmol) at 0°C. The whole mixture was stirred at room temperature for 0.5 h and then was concentrated under reduced pressure to leave a grayish solid residue. Acetone (50 ml) was added to the residue. After removal of undissolved solid (NaF) by filtration, diethyl ether (200 ml) was added to the filtrate to precipitate a white solid, which was collected as analytically pure salt **2a** (5.632 g, 78% yield).

The other polyfluoroalkoxylated ammonium iodides **2b**, **2c**, and **2d** were prepared in a similar way cited above.

The reaction of **1** (5.621 g, 20.0 mmol) with 2,2,2-trifluoroethanol (4.500 g, 45.0 mmol) and sodium hydride (1.080 g, 45.0 mmol) was carried out under the same conditions as cited above. To the reaction mixture were added water and dichloromethane. The dichloromethane layer was separated, dried over anhydrous sodium sulfate, and carefully concentrated under reduced pressure. The resulting residue was chromatographed on a silica gel column (ethyl acetate) to give 1,2-bis(2,2,2-trifluoroethoxy)-3,3-difluoro-1-propene: 75% yield. ¹H NMR (CDCl₃) δ: 4.23 (q, *J* = 8.1 Hz, 2H), 4.36 (q, *J* = 8.3 Hz, 2H), 5.90 (t, *J* = 54.1 Hz, 1H), 6.18 (s, 1H) ppm. ¹⁹F NMR (CDCl₃) δ: -121.70 (d, *J* = 54.1 Hz, 2F), -75.95 (t, *J* = 8.3 Hz, 3F), -75.66 (t, *J* = 8.1 Hz, 3F) ppm. MS (EI) *m/z*: 274 (M), 255, 191, 83. Although the formation of a small amount of **2a** was observed by ¹⁹F NMR of the reaction mixture, the isolation was not tried in this experiment.

N-[2-(2,2,2-Trifluoroethoxy)-3,3-difluoro-1-propenyl]trimethylammonium iodide (**2a**): Mp: 117–118°C. IR (KBr) (cm⁻¹): 2975, 1705, 1460, 1380, 1035, 965. ¹H NMR (DMSO-*d*₆) δ: 3.45 (s, 9H), 4.95 (q, *J* = 8.5 Hz, 2H), 6.55 (t, *J* = 1.7 Hz, 1H), 6.80 (t, *J* = 51.6 Hz, 1H) ppm. ¹⁹F NMR (DMSO-*d*₆) δ: -119.40 (d, *J* = 51.6 Hz, 2F), -73.18 (t,

J = 8.5 Hz, 3F) ppm. MS (SIMS) *m/z*: 595 (2M - I⁻), 234 (M - I⁻), 200, 136.

N-[2-(2,2,3,3,3-Pentafluoropropoxy)-3,3-difluoro-1-propenyl]trimethylammonium iodide (**2b**): Mp: 118–119°C. IR (KBr) (cm⁻¹): 3015, 1705, 1472, 1381, 1240, 1045, 982. ¹H NMR (DMSO-*d*₆) δ: 3.47 (s, 9H), 5.02 (brt, *J* = 13.2 Hz, 2H), 6.58 (brs, 1H), 6.83 (t, *J* = 51.4 Hz, 1H) ppm. ¹⁹F NMR (DMSO-*d*₆) δ: -123.31 (t, *J* = 13.2 Hz, 2F), -119.41 (d, *J* = 51.4 Hz, 2F), -82.73 (s, 3F) ppm. MS (SIMS) *m/z*: 695 (2M - I⁻), 284 (M - I⁻), 250, 136.

N-[2-(2,2,3,3-Tetrafluoropropoxy)-3,3-difluoro-1-propenyl]trimethylammonium iodide (**2c**): Mp: 110–111°C. IR (KBr) (cm⁻¹): 3001, 1701, 1474, 1389, 1248, 1042, 984. ¹H NMR (DMSO-*d*₆) δ: 3.46 (s, 9H), 4.82 (brt, *J* = 13.7 Hz, 2H), 6.54 (brs, 1H), 6.74 (tt, *J* = 51.7, 5.1 Hz, 1H), 6.82 (t, *J* = 51.4 Hz, 1H) ppm. ¹⁹F NMR (DMSO-*d*₆) δ: -138.22 (dt, *J* = 51.7, 5.1 Hz, 2F), -124.96 (m, 2F), -118.95 (d, *J* = 51.4 Hz, 2F) ppm. MS (SIMS) *m/z*: 659 (2M - I⁻), 266 (M - I⁻), 232, 136.

N-[2-(2,2,3,3,4,4,5,5-Octafluoropentoxy)-3,3-difluoro-1-propenyl]trimethylammonium iodide (**2d**): Mp: 96–97°C. IR (KBr) (cm⁻¹): 3018, 1701, 1489, 1381, 1263, 1036, 974. ¹H NMR (DMSO-*d*₆) δ: 3.52 (s, 9H), 4.97 (brt, *J* = 13.8 Hz, 2H), 6.63 (brs, 1H), 6.80 (t, *J* = 51.7 Hz, 1H), 6.90 (tt, *J* = 50.5, 5.4 Hz, 1H) ppm. ¹⁹F NMR (DMSO-*d*₆) δ: -138.13 (dm, *J* = 50.5 Hz, 2F), -129.17 (m, 2F), -124.20 (m, 2F), -119.73 (brt, *J* = 11.8 Hz, 2F), -119.15 (d, *J* = 51.7 Hz, 2F) ppm. MS (SIMS) *m/z*: 859 (2M - I⁻), 366 (M - I⁻), 332, 136.

3.2.2. Preparation of β-polyfluoroalkoxy vinamidinium salts **3** and/or **4** from isolated ammonium iodides **2**

To a mixture of the ammonium iodide **2a** (3.610 g, 10.0 mmol) and molecular sieves 4A (10.0 g) in MeCN (20 ml) was gradually added diethylamine (3.657 g, 50.0 mmol) at room temperature and then the mixture was stirred at 70°C for 1 h. After cooling to room temperature, water (30 ml) and methylene chloride (30 ml) were added. The methylene chloride layer was separated and the aqueous layer was extracted with methylene chloride (2 × 30 ml). The methylene chloride layers were combined, washed with brine (30 ml) and dried over Na₂SO₄. After evaporating the solvent, the resulting residue was chromatographed on a silica gel column (ethyl acetate and then ethanol) to give β-trifluoroethoxy vinamidinium salt **3a-Et** (2.407 g, 59% yield) and **4a-Et** (0.988 g, 26% yield).

The reactions of the other ammonium iodides **2b**, **2c** and **2d** with diethylamine were carried out in the same manner as cited above. The formed β-polyfluoroalkoxy vinamidinium salts **3-Et** and **4-Et** could not be separated by column chromatography. The ratios of **3** and **4**, shown in Table 1, were determined with ¹H and ¹⁹F NMR spectra of the reaction mixtures. Each of the signals in NMR spectra of the mixture could clearly be assigned to either the salt **3** or **4**.

1,1,5,5-Tetraethyl-3-(2,2,2-trifluoroethoxy)-1,5-diaza-1,3-pentadienium iodide (**3a-Et**): Mp: 104–105°C. IR

(KBr) (cm^{-1}): 2978, 1654, 1597, 1443, 1315, 1265, 1061, 988. ^1H NMR (CDCl_3) δ : 1.29 (t, $J=7.2$ Hz, 6H), 1.41 (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) ppm. ^{19}F NMR (CDCl_3) δ : -73.75 (t, $J=8.2$ Hz, 3F) ppm. ^{13}C NMR (CDCl_3) δ : 13.57 (s), 14.67 (s), 44.41 (s), 52.71 (s), 70.52 (q, $J=33.8$ Hz), 122.33 (q, $J=278.3$ Hz), 123.66 (s), 155.50 (s) ppm. MS (SIMS) m/z : 689 ($2\text{M}-\text{I}^-$), 281 ($\text{M}-\text{I}^-$), 208, 125. Analysis: Calc. for $\text{C}_{13}\text{H}_{24}\text{N}_2\text{OF}_3\text{I}$: C, 38.23; H, 5.93; F, 13.97%. Found: C, 38.44; H, 6.00; F, 13.90%.

1,1-Diethyl-5,5-dimethyl-3-(2,2,2-trifluoroethoxy)-1,5-diaza-1,3-pentadienium iodide (**4a-Et**): Mp: 132–133°C. IR (KBr) (cm^{-1}): 2978, 1663, 1612, 1420, 1312, 1269, 1061, 964. ^1H NMR (CDCl_3) δ : 1.30 (t, $J=7.2$ Hz, 3H), 1.40 (t, $J=7.2$ Hz, 3H), 3.479 (s, 3H), 3.482 (s, 3H), 3.65 (q, $J=7.2$ Hz, 2H), 3.74 (q, $J=7.2$ Hz, 2H), 4.21 (q, $J=8.3$ Hz, 2H), 8.10 (s, 1H), 8.30 (s, 1H) ppm. ^{13}C NMR (CDCl_3) δ : 13.49 (s), 14.64 (s), 39.25 (s), 44.36 (s), 47.99 (s), 52.72 (s), 70.79 (q, $J=34.0$ Hz), 120.89 (q, $J=278.3$ Hz), 123.98 (s), 135.08 (s), 157.65 (s) ppm. ^{19}F NMR (CDCl_3) δ : -73.42 (t, $J=8.3$ Hz, 3F) ppm. MS (SIMS) m/z : 633 ($2\text{M}-\text{I}^-$), 253 ($\text{M}-\text{I}^-$), 208, 125.

1,1,5,5-Tetraethyl-3-(2,2,3,3,3-pentafluoropropoxy)-1,5-diaza-1,3-pentadienium iodide (**3b-Et**): ^1H NMR (CDCl_3) δ : 1.29 (t, $J=7.2$ Hz, 6H), 1.41 (t, $J=7.2$ Hz, 6H), 3.65–3.75 (m, 8H), 4.10 (t, $J=13.5$ Hz, 2H), 8.52 (s, 2H) ppm. ^{19}F NMR (CDCl_3) δ : -123.65 (t, $J=13.5$ Hz, 2F), -84.01 (s, 3F) ppm.

1,1-Diethyl-5,5-dimethyl-3-(2,2,3,3,3-pentafluoropropoxy)-1,5-diaza-1,3-pentadienium iodide (**4b-Et**): ^1H NMR (CDCl_3) δ : 1.29 (t, $J=7.2$ Hz, 3H), 1.40 (t, $J=7.2$ Hz, 3H), 3.41 (s, 3H), 3.48 (s, 3H), 3.65–3.75 (m, 4H), 4.16 (t, $J=13.5$ Hz, 2H), 8.33 (s, 1H), 8.57 (s, 1H) ppm. ^{19}F NMR (CDCl_3) δ : -123.49 (t, $J=13.5$ Hz, 2F), -83.93 (s, 3F) ppm.

1,1,5,5-Tetraethyl-3-(2,2,3,3-tetrafluoropropoxy)-1,5-diaza-1,3-pentadienium iodide (**3c-Et**): ^1H NMR (CDCl_3) δ : 1.28 (t, $J=7.2$ Hz, 6H), 1.40 (t, $J=7.2$ Hz, 6H), 3.65–3.75 (m, 8H), 4.11 (t, $J=14.0$ Hz, 2H), 6.11 (tt, $J=52.9$, 3.5 Hz, 1H), 8.40 (s, 2H) ppm. ^{19}F NMR (CDCl_3) δ : -137.05 (d, $J=52.9$ Hz, 2F), -123.28 (td, $J=14.0$, 3.5 Hz, 2F) ppm.

1,1-Diethyl-5,5-dimethyl-3-(2,2,3,3-tetrafluoropropoxy)-1,5-diaza-1,3-pentadienium iodide (**4c-Et**): ^1H NMR (CDCl_3) δ : 1.28 (t, $J=7.2$ Hz, 3H), 1.40 (t, $J=7.2$ Hz, 3H), 3.45 (s, 3H), 3.46 (s, 3H), 3.65–3.75 (m, 4H), 4.18 (t, $J=14.0$ Hz, 2H), 6.17 (tt, $J=52.9$, 3.5 Hz, 1H), 8.21 (s, 1H), 8.43 (s, 1H) ppm. ^{19}F NMR (CDCl_3) δ : -137.05 (t, $J=52.9$ Hz, 2F), -123.28 (td, $J=14.0$, 3.5 Hz, 2F) ppm.

1,1,5,5-Tetraethyl-3-(2,2,3,3,4,4,5,5-octafluoropentoxy)-1,5-diaza-1,3-pentadienium iodide (**3d-Et**): ^1H NMR (CDCl_3) δ : 1.29 (t, $J=7.2$ Hz, 6H), 1.41 (t, $J=7.2$ Hz, 6H), 3.65–3.75 (m, 8H), 4.12 (t, $J=14.7$ Hz, 2H), 6.13 (tt, $J=51.9$, 5.1 Hz, 1H), 8.51 (s, 2H) ppm. ^{19}F NMR (CDCl_3) δ : -137.49 (dm, $J=51.9$, 2F), -129.66 (m, 2F), -125.40 (m, 2F), -120.48 (m, 2F) ppm.

1,1-Diethyl-5,5-dimethyl-3-(2,2,3,3,4,4,5,5-octafluoropentoxy)-1,5-diaza-1,3-pentadienium iodide (**4d-Et**): ^1H NMR (CDCl_3) δ : 1.29 (t, $J=7.2$ Hz, 3H), 1.40 (t, $J=7.2$ Hz, 3H), 3.41 (s, 3H), 3.48 (s, 3H), 3.65–3.75 (m, 4H), 4.17 (t, $J=14.7$ Hz, 2H), 6.13 (tt, $J=51.9$, 5.1 Hz, 1H), 8.33 (s, 1H), 8.56 (s, 1H) ppm. ^{19}F NMR (CDCl_3) δ : -137.49 (dm, $J=51.9$ Hz, 2F), -129.66 (m, 2F), -125.40 (m, 2F), -120.48 (m, 2F) ppm.

3.2.3. One-pot preparation of β -polyfluoroalkoxy vinamidinium salts **3** and/or **4** from the ammonium iodide **1**

To a mixture of the ammonium iodide **1** (2.810 g, 10.0 mmol), 2,2,2-trifluoroethanol (1.100 g, 11.0 mmol) and molecular sieves 4A (10.0 g) in MeCN (30 ml) was gradually added sodium hydride (0.264 g, 11.0 mmol) at 0°C and the mixture was stirred at room temperature for 0.5 h. Successively, diethylamine (3.657 g, 50.0 mmol) was added at room temperature and then the mixture was heated at 70°C for 1 h with stirring. After cooling to room temperature, the reaction mixture was worked up in the same manner as described in Section 3.2.2 to give the vinamidinium salt **3a-Et** (2.040 g, 50% yield) and **3a-Et** (0.760 g, 20% yield).

The one-pot reactions using other polyfluoroalcohols and secondary amines, such as diethylamine, diisopropylamine, pyrrolidine, piperidine and morpholine, were carried out similarly. The yields and ratios of **3** to **4** are summarized in Table 1.

1,1-Dimethyl-5,5-diisopropyl-3-(2,2,2-trifluoroethoxy)-1,5-diaza-1,3-pentadienium iodide (**4a-i-Pr**): Mp: 206–208°C. IR (KBr) (cm^{-1}): 2970, 2934, 1665, 1595, 1437, 1207, 1111, 922, 764, 679. ^1H NMR (CDCl_3) δ : 1.33 (d, $J=6.6$ Hz, 6H), 1.54 (d, $J=6.6$ Hz, 6H), 3.42 (s, 3H), 3.51 (s, 3H), 3.87 (h, $J=6.6$ Hz, 1H), 4.087 (q, $J=7.5$ Hz, 2H), 5.05 (h, $J=6.6$ Hz, 1H), 7.97 (s, 2H), 8.96 (s, 1H) ppm. ^{19}F NMR (CDCl_3) δ : -74.02 (t, $J=7.5$ Hz, 3F) ppm. MS (SIMS) m/z : 689 ($2\text{M}-\text{I}^-$), 281 ($\text{M}-\text{I}^-$), 180, 97.

1,3-Dipyrrolidino-2-(2,2,2-trifluoroethoxy)-1,3-propadienium iodide (**3a-Py**): Mp: 214–215°C. IR (KBr) (cm^{-1}): 2964, 2876, 1593, 1435, 1278, 1159, 1126, 1057, 870, 680. ^1H NMR (CDCl_3) δ : 2.04 (m, 8H), 3.81 (t, $J=6.9$ Hz, 4H), 3.92 (t, $J=6.9$ Hz, 4H), 4.18 (q, $J=8.4$ Hz, 2H), 8.33 (s, 2H) ppm. ^{19}F NMR (CDCl_3) δ : -73.18 (t, $J=8.4$ Hz, 3F) ppm. MS (SIMS) m/z : 681 ($2\text{M}-\text{I}^-$), 277 ($\text{M}-\text{I}^-$), 206, 124. Analysis: Calc. for $\text{C}_{13}\text{H}_{20}\text{N}_2\text{OF}_3\text{I}$: C, 38.61; H, 4.99; F, 14.11%. Found: C, 38.47; H, 4.98; F, 14.19%.

1,3-Dipyrrolidino-2-(2,2,3,3,3-pentafluoropropoxy)-1,3-propadienium iodide (**3b-Py**): Mp: 226–227°C. IR (KBr) (cm^{-1}): 2963, 2876, 1593, 1437, 1269, 1213, 1126, 1057, 690. ^1H NMR (CDCl_3) δ : 2.03 (m, 8H), 3.75 (t, $J=6.9$ Hz, 4H), 3.93 (t, $J=6.9$ Hz, 4H), 4.13 (t, $J=13.8$ Hz, 2H), 8.55 (s, 2H) ppm. ^{19}F NMR (CDCl_3) δ : -122.94 (t, $J=13.8$ Hz, 2F), -83.96 (s, 3F) ppm. MS (SIMS) m/z : 781 ($2\text{M}-\text{I}^-$), 327 ($\text{M}-\text{I}^-$), 256, 124.

1,3-Dipyrrolidino-2-(2,2,3,3-tetrafluoropropoxy)-1,3-propadienium iodide (**3c-Py**): Mp: 184–185°C. IR (KBr)

(cm^{-1}): 2951, 2880, 1593, 1452, 1269, 1196, 1099, 1061, 831, 702. $^1\text{H NMR}$ (CDCl_3) δ : 2.03 (m, 8H), 3.79 (t, $J=6.9$ Hz, 4H), 3.92 (t, $J=6.9$ Hz, 4H), 4.12 (t, $J=14.1$ Hz, 2H), 5.99 (tt, $J=53.1, 3.6$, 1H), 8.46 (s, 2H) ppm. $^{19}\text{F NMR}$ (CDCl_3) δ : -137.12 (d, $J=53.1$ Hz, 2F), -122.55 (t, $J=14.1$ Hz, 2F) ppm. MS (SIMS) m/z : 745 ($2\text{M}-\text{I}^-$), 309 ($\text{M}-\text{I}^-$), 238, 124.

1,3-Dipyrrolidino-2-(2,2,3,3,4,4,5,5-octafluoropentoxy)-1,3-propadienium iodide (**3d-Py**): Mp: 139–141°C. IR (KBr) (cm^{-1}): 2966, 2878, 1589, 1448, 1269, 1169, 1126, 1086, 808, 727. $^1\text{H NMR}$ (CDCl_3) δ : 2.04 (m, 8H), 3.77 (t, $J=6.9$ Hz, 4H), 3.94 (t, $J=6.9$ Hz, 4H), 4.20 (t, $J=15.0$ Hz, 2H), 6.10 (tt, $J=51.8, 5.2$ Hz, 1H), 8.45 (s, 2H) ppm. $^{19}\text{F NMR}$ (CDCl_3) δ : -137.50 (dm, $J=51.8$ Hz, 2F), -129.71 (m, 2F), -125.25 (m, 2F), -119.62 (m, 2F) ppm. MS (SIMS) m/z : 945 ($2\text{M}-\text{I}^-$), 409 ($\text{M}-\text{I}^-$), 338, 124.

1,3-Dipiperidino-2-(2,2,2-trifluoroethoxy)-1,3-propadienium iodide (**3a-Pi**): Mp: 176–178°C. IR (KBr) (cm^{-1}): 2928, 2862, 1601, 1447, 1269, 1211, 1171, 1099, 891, 678. $^1\text{H NMR}$ (CDCl_3) δ : 1.76 (m, 12H), 3.77 (m, 4H), 3.94 (m, 4H), 4.08 (q, $J=8.4$ Hz, 2H), 8.32 (s, 2H) ppm. $^{19}\text{F NMR}$ (CDCl_3) δ : -73.86 (t, $J=8.4$ Hz, 2F) ppm. MS (SIMS) m/z : 738 ($2\text{M}-\text{I}^-$), 305 ($\text{M}-\text{I}^-$), 220, 137.

1,3-Dimorpholino-2-(2,2,2-trifluoroethoxy)-1,3-propadienium iodide (**3a-Mo**): Mp: 211–213°C. IR (KBr) (cm^{-1}): 2980, 2850, 1601, 1458, 1277, 1213, 1169, 1063, 861, 680. $^1\text{H NMR}$ (CDCl_3) δ : 3.88 (m, 16H), 4.09 (q, $J=8.2$ Hz, 2H), 8.64 (s, 2H) ppm. $^{19}\text{F NMR}$ (CDCl_3) δ : -73.60 (t, $J=8.2$ Hz, 3F) ppm. MS (SIMS) m/z : 745 ($2\text{M}-\text{I}^-$), 309 ($\text{M}-\text{I}^-$), 222, 139. Analysis: Calc. for $\text{C}_{13}\text{H}_{20}\text{F}_3\text{N}_2\text{O}_3\text{I}$: C, 35.78; H, 4.62; F, 13.07%. Found: C, 35.81; H, 4.75; F, 12.66%.

3.3. Synthesis of polyfluoroalkoxylated heterocycles

3.3.1. Synthesis of 5-polyfluoroalkoxylated pyrimidines 6 from isolated vinamidinium salts 3 (4)

To a mixture of the vinamidinium salt **3a** (**4a**)-Et (mixture of **3a** and **4a** (69:31), 0.400 g, 1.0 mmol), benzamidine hydrochloride (**5i**) (0.235 g, 1.5 mmol) and molecular sieves 4A (1.0 g) in MeCN (1 ml) was gradually added a 28 wt.% methanol solution of sodium methylate (0.289 g, 1.5 mmol) and then the mixture was stirred at room temperature for 3 h. Water (20 ml) and methylene chloride (20 ml) were added. The methylene chloride layer was separated and the aqueous layer was extracted with methylene chloride (2×20 ml). The methylene chloride layers were combined, washed with brine (30 ml) and dried over Na_2SO_4 . After evaporating the solvent, the resulting residue was chromatographed on a silica gel column (benzene–ethyl acetate/1:1) to give 2-phenyl-5-(2,2,2-trifluoroethoxy)pyrimidine (**6a-i**) (0.299 g, 90% yield).

The reactions between the vinamidinium salts **3a** (**4a**)-Et, **3a-Py** or **3a-Mo** and various amidinium salts **5ii–vii** were

carried out in the same manner as described above. The results of the reactions are summarized in Table 2.

2-Phenyl-5-(2,2,2-trifluoroethoxy)pyrimidine (**6a-i**): Mp: 132–133°C. IR (KBr) (cm^{-1}): 1578, 1560, 1286, 1171, 1084, 1057, 976, 746, 696. $^1\text{H NMR}$ (CDCl_3) δ : 4.46 (q, $J=7.9$ Hz, 2H), 7.47 (m, 3H), 8.36 (m, 2H), 8.51 (s, 2H) ppm. $^{19}\text{F NMR}$ (CDCl_3) δ : -74.33 (t, $J=7.9$ Hz, 3F) ppm. $^{13}\text{C NMR}$ (CDCl_3) δ : 66.38 (q, $J=36.3$ Hz), 122.72 (q, $J=278.7$ Hz), 127.76 (s), 128.55 (s), 130.24 (s), 136.86 (s), 144.50 (s), 150.18 (s), 159.55 (s) ppm. MS (EI) m/z (rel. intensity): 254 (M^+ , 100), 144 (44), 116 (62), 103 (16), 89 (26). HRMS (EI): Calc. for $\text{C}_{12}\text{H}_9\text{F}_3\text{N}_2\text{O}$: 254.0667. Found: 254.0661. Analysis: Calc. for $\text{C}_{12}\text{H}_9\text{N}_2\text{OF}_3$: C, 56.68; H, 3.57; F, 22.43%. Found: C, 56.52; H, 3.50; F, 22.46%.

5-(2,2,2-Trifluoroethoxy)pyrimidine (**6a-ii**): Liquid. IR (neat) (cm^{-1}): 3051, 1629, 1566, 1421, 1298, 1171, 1119, 1060, 866, 719, 689. $^1\text{H NMR}$ (CDCl_3) δ : 4.51 (q, $J=7.8$ Hz, 2H), 8.51 (s, 2H), 8.96 (s, 1H) ppm. $^{19}\text{F NMR}$ (CDCl_3) δ : -74.32 (t, $J=7.8$ Hz, 3F) ppm. MS (EI) m/z (rel. intensity): 178 (M^+ , 100), 124 (21), 109 (21). HRMS (EI): Calc. for $\text{C}_6\text{H}_5\text{F}_3\text{N}_2\text{O}$: 178.0354. Found: 178.0347.

2-Methyl-5-(2,2,2-trifluoroethoxy)pyrimidine (**6a-iii**): Mp: 28–29°C. IR (KBr) (cm^{-1}): 3055, 2915, 1560, 1452, 1304, 1261, 1175, 1070, 868, 740, 667. $^1\text{H NMR}$ (CDCl_3) δ : 2.71 (s, 3H), 4.44 (q, $J=7.8$ Hz, 2H), 8.39 (s, 2H) ppm. $^{19}\text{F NMR}$ (CDCl_3) δ : -74.42 (t, $J=7.8$ Hz, 3F) ppm. MS (EI) m/z (rel. intensity): 192 (M^+ , 100), 178 (7), 146 (7), 109 (5), 97 (4). HRMS (EI): Calc. for $\text{C}_7\text{H}_7\text{F}_3\text{N}_2\text{O}$: 192.0511. Found: 192.0510.

2-Amino-5-(2,2,2-trifluoroethoxy)pyrimidine (**6a-iv**): Mp: 118–119°C. IR (KBr) (cm^{-1}): 3327, 3192, 1647, 1568, 1489, 1458, 1256, 1163, 856, 656. $^1\text{H NMR}$ (CDCl_3) δ : 4.62 (q, $J=8.1$ Hz, 2H), 5.18 (brs, 2H), 8.12 (s, 2H) ppm. $^{19}\text{F NMR}$ (CDCl_3) δ : -74.64 (t, $J=8.1$ Hz, 3F) ppm. MS (EI) m/z (rel. intensity): 194 (M^+ , 100), 177 (7), 110 (6), 82 (7), 73 (4). HRMS (CI): Calc. for $\text{C}_6\text{H}_7\text{F}_3\text{N}_3\text{O}$: 194.0542. Found: 194.0536 ($\text{M}^+ + \text{H}$).

2-(Methylamino)-5-(2,2,2-trifluoroethoxy)pyrimidine (**6a-v**): Mp: 94–95°C. IR (KBr) (cm^{-1}): 3300, 3152, 3109, 2949, 1618, 1589, 1458, 1252, 1163, 1078, 1065, 864, 650. $^1\text{H NMR}$ (CDCl_3) δ : 2.97 (d, $J=5.1$ Hz, 3H), 4.29 (q, $J=8.1$ Hz, 2H), 5.52 (brs, 1H), 8.13 (s, 2H) ppm. $^{19}\text{F NMR}$ (CDCl_3) δ : -74.68 (t, $J=8.1$ Hz, 3F) ppm. MS (EI) m/z (rel. intensity): 207 (M^+ , 100), 179 (19), 124 (57), 96 (2). HRMS (EI): Calc. for $\text{C}_7\text{H}_8\text{F}_3\text{N}_3\text{O}$: 207.0620. Found: 207.0613.

2-Methoxy-5-(2,2,2-trifluoroethoxy)pyrimidine (**6a-vi**): Mp: 49–50°C. IR (KBr) (cm^{-1}): 3065, 2990, 1570, 1493, 1433, 1312, 1288, 1265, 1067, 1040, 1024, 972, 876, 787, 675. $^1\text{H NMR}$ (CDCl_3) δ : 3.99 (s, 3H), 4.20 (q, $J=8.0$ Hz, 2H), 8.30 (s, 2H) ppm. $^{19}\text{F NMR}$ (CDCl_3) δ : -74.54 (t, $J=8.0$ Hz, 3F) ppm. MS (EI) m/z (rel. intensity): 208 (M^+ , 100), 178 (76), 166 (6), 125 (22), 109 (8), 97 (19), 80 (16), 70 (15). HRMS (EI): Calc. for $\text{C}_7\text{H}_7\text{F}_3\text{N}_4\text{O}$: 208.0460. Found: 208.0452.

2-Methylthio-5-(2,2,2-trifluoroethoxy)pyrimidine (**6a-vii**): Mp: 62–63°C. IR (KBr) (cm^{-1}): 3045, 2937, 1551, 1508, 1458, 1387, 1302, 1281, 1302, 1281, 1263, 1178, 1161, 972, 762, 635. ^1H NMR (CDCl_3) δ : 2.56 (s, 3H), 4.42 (q, $J=7.9$ Hz, 2H), 8.33 (s, 3H) ppm. ^{19}F NMR (CDCl_3) δ : –74.40 (t, $J=7.9$ Hz, 3F) ppm. MS (EI) m/z (rel. intensity): 224 (M^+ , 100), 191 (4), 178 (23), 141 (91), 109 (7), 99 (9), 91 (3), 80 (9). HRMS (EI): Calc. for $\text{C}_7\text{H}_7\text{F}_3\text{N}_2\text{OS}$: 224.0232. Found: 224.0231.

5-(2,2,3,3,3-Pentafluoropropoxy)-2-phenylpyrimidine (**6b-i**): Mp: 126–127°C. IR (KBr) (cm^{-1}): 1555, 1439, 1283, 1248, 1209, 1198, 1150, 1105, 1084, 949, 750, 675. ^1H NMR (CDCl_3) δ : 4.54 (tq, $J=12.0, 0.9$ Hz, 2H), 7.47 (m, 3H), 8.37 (m, 2H), 8.52 (s, 2H) ppm. ^{19}F NMR (CDCl_3) δ : –123.75 (t, $J=12.0$ Hz, 2F), –83.83 (m, 3F) ppm. MS (EI) m/z (rel. intensity): 304 (M^+ , 100), 171 (3), 116 (48), 103 (26), 89 (16), 77 (4), 63 (6): HRMS (EI): Calc. for $\text{C}_{13}\text{H}_9\text{F}_5\text{N}_2\text{O}$: 304.0635. Found: 304.0639.

2-Phenyl-5-(2,2,3,3-tetrafluoropropoxy)pyrimidine (**6c-i**): Mp: 117–118°C. IR (KBr) (cm^{-1}): 1578, 1560, 1441, 1394, 1286, 1248, 1227, 1205, 1184, 1130, 1109, 1078, 1051, 835, 748, 691. ^1H NMR (CDCl_3) δ : 4.48 (tt, $J=11.9, 1.4$ Hz, 2H), 6.03 (tt, $J=53.1, 4.2$ Hz, 2H), 7.47 (m, 3H), 8.37 (m, 2H), 8.51 (s, 2H) ppm. ^{19}F NMR (CDCl_3) δ : –138.72 (dtt, $J=53.1, 3.3, 1.4$ Hz, 2F), –124.54 (tdt, $J=11.9, 4.2, 3.3$ Hz, 2F) ppm. MS (EI) m/z (rel. intensity): 286 (M^+ , 100), 171 (5), 144 (44), 116 (52), 103 (8), 89 (21), 77 (4): HRMS (EI): Calc. for $\text{C}_{13}\text{H}_{10}\text{F}_4\text{N}_2\text{O}$: 286.0730. Found: 286.0733.

5-(2,2,3,3,4,4,5,5-Octafluoropentoxy)-2-phenylpyrimidine (**6d-i**): Mp: 96–97°C. IR (KBr) (cm^{-1}): 1556, 1445, 1317, 1279, 1248, 1234, 1173, 1128, 1088, 1074, 970, 812, 768, 750, 696. ^1H NMR (CDCl_3) δ : 4.58 (brt, $J=12.8$ Hz, 2H), 6.08 (tt, $J=51.9, 5.4$ Hz, 1H), 7.47 (m, 3H), 8.37 (m, 2H), 8.52 (s, 2H) ppm. ^{19}F NMR (CDCl_3) δ : –137.57 (dm, $J=51.9$ Hz, 2F), –130.23 (m, 2F), –125.45 (m, 2F), –120.07 (m, 2F) ppm. MS (EI) m/z (rel. intensity): 386 (M^+ , 98), 340 (6), 171 (7), 144 (59), 116 (100). HRMS (EI): Calc. for $\text{C}_{15}\text{H}_{10}\text{F}_8\text{N}_2\text{O}$: 386.0666. Found: 386.0657.

3.3.2. Synthesis of 4-trifluoroethoxylated pyrazoles **8** from isolated vinamidinium salts **3** (**4**)

To a mixture of the vinamidinium salt **3a** (**4a**)-Et (mixture of **3a** and **4a** (69:31), 0.400 g, 1.0 mmol) and molecular sieves 4A (1.0 g) in MeCN (1 ml) was gradually added methylhydrazine (**7iii**) (97% purity, 0.071 g, 1.5 mmol) and then the mixture was stirred at room temperature for 3 h. Water (20 ml) and methylene chloride (20 ml) were added. The methylene chloride layer was separated and the aqueous layer was extracted with methylene chloride (2×20 ml). The methylene chloride layers were combined, washed with brine (30 ml) and dried over Na_2SO_4 . After removal of the solvent, the residue was chromatographed on a silica gel column (benzene–ethyl acetate/4:1) to give 1-methyl-4-

(2,2,2-trifluoroethoxy)pyrazole (**8a-iii**) (0.153 g, 85% yield).

The reaction of the vinamidinium salts **3a** (**4a**)-Et with hydrazine (**7ii**) or phenylhydrazine (**7i**) and the reaction of **3c** (**4c**)-Et or **3d** (**4d**)-Et with **7iii** were carried out in the same manner as described above. The starting salts were completely consumed in all reactions except the reaction with **7i**. The reactions with **7i** at room temperature hardly proceeded, the vinamidinium salts being recovered in 77% but the reaction at 70°C gave **8i** (44% yield), along with the starting salts (15% recovered) and unidentified products.

1-Phenyl-4-(2,2,2-trifluoroethoxy)pyrazole (**8a-i**): Mp: 64–65°C. IR (KBr) (cm^{-1}): 3123, 1597, 1580, 1506, 1462, 1400, 1366, 1279, 1265, 1188, 1163, 1099, 970, 953, 758, 691. ^1H NMR (CDCl_3) δ : 4.29 (q, $J=8.2$ Hz, 2H), 7.27 (m, 1H), 7.43 (m, 2H), 7.52 (s, 1H), 7.61 (m, 2H), 7.67 (s, 1H) ppm. ^{19}F NMR (CDCl_3) δ : –74.72 (t, $J=8.2$ Hz, 3F) ppm. MS (EI) m/z (rel. intensity): 242 (M^+ , 100), 159 (22), 132 (8), 104 (100), 77 (100). HRMS (EI): Calc. for $\text{C}_{11}\text{H}_9\text{F}_3\text{N}_2\text{O}$: 242.0667. Found: 242.0664.

4-(2,2,2-Trifluoroethoxy)pyrazole (**8a-ii**): Mp: 40–41°C. IR (KBr) (cm^{-1}): 3157, 3126, 2990, 2966, 1589, 1360, 1267, 1182, 1165, 1096, 972, 627. ^1H NMR (CDCl_3) δ : 4.18 (q, $J=8.3$ Hz, 2H), 7.31 (s, 2H), 10.63 (brs, 1H) ppm. ^{19}F NMR (CDCl_3) δ : –74.82 (t, $J=8.3$ Hz, 3F) ppm. ^{13}C NMR (CDCl_3) δ : 69.92 (q, $J=35.3$ Hz), 121.88 (q, $J=278.7$ Hz), 144.75 (br s) ppm. MS (EI) m/z (rel. intensity): 166 (M^+ , 100), 113 (4), 83 (66). HRMS (EI): Calc. for $\text{C}_5\text{H}_5\text{F}_3\text{N}_2\text{O}$: 166.0354. Found: 166.0354. Analysis: Calc. for $\text{C}_5\text{H}_5\text{F}_3\text{N}_2\text{O}$: C, 36.14; H, 3.03; F, 34.33%. Found: C, 36.19; H, 3.04; F, 34.11%.

1-Methyl-4-(2,2,2-trifluoroethoxy)pyrazole (**8a-iii**): Liquid. IR (neat) (cm^{-1}): 3123, 2949, 1576, 1447, 1404, 1358, 1277, 1163, 1080, 1011, 966, 858, 831, 694, 683, 654. ^1H NMR (CDCl_3) δ : 3.82 (s, 3H), 4.22 (q, $J=8.3$ Hz, 2H), 7.15 (s, 1H), 7.26 (s, 1H) ppm. ^{19}F NMR (CDCl_3) δ : –74.87 (t, $J=8.3$ Hz, 3F) ppm. MS (EI) m/z (rel. intensity): 180 (M^+ , 100), 105 (3), 97 (52), 78 (14), 68 (3). HRMS (EI): Calc. for $\text{C}_6\text{H}_7\text{F}_3\text{N}_2\text{O}$: 180.0511. Found: 180.0504.

1-Methyl-4-(2,2,3,3-tetrafluoropropoxy)pyrazole (**8c-iii**): Liquid. IR (neat) (cm^{-1}): 3125, 2949, 1578, 1448, 1404, 1356, 1231, 1205, 1109, 1072, 835, 691. ^1H NMR (CDCl_3) δ : 3.82 (s, 3H), 4.23 (tt, $J=12.2, 1.5$ Hz, 2H), 6.00 (tt, $J=53.1, 4.8$ Hz, 1H), 7.13 (s, 1H), 7.24 (s, 1H) ppm. ^{19}F NMR (CDCl_3) δ : –139.82 (dtt, $J=53.1, 4.1, 1.5$ Hz, 2F), –125.77 (tdt, $J=12.2, 4.8, 4.1$ Hz, 2F) ppm. MS (EI) m/z (rel. intensity): 212 (M^+ , 100), 113 (3), 97 (73). HRMS (EI): Calc. for $\text{C}_7\text{H}_8\text{F}_4\text{N}_2\text{O}$: 212.0573. Found: 212.0581.

1-Methyl-4-(2,2,3,3,4,4,5,5-octafluoropentoxy)pyrazole (**8d-iii**): Liquid. IR (neat) (cm^{-1}): 3005, 2951, 1578, 1448, 1404, 1356, 1173, 1130, 1082, 982, 810, 652. ^1H NMR (CDCl_3) δ : 3.83 (s, 3H), 4.34 (tt, $J=13.4, 1.5$ Hz, 2H), 6.07 (tt, $J=52.0, 5.4$ Hz, 1H), 7.16 (s, 1H), 7.27 (s, 1H) ppm. ^{19}F NMR (CDCl_3) δ : –137.70 (brd, $J=52.0$ Hz, 2F),

–130.58 (brs, 2F), –125.87 (brs, 2F), –120.59 (brs, 2F) ppm. MS (EI) m/z (rel. intensity): 312 (M^+ , 100), 162 (7), 151 (8), 113 (7), 97 (62). HRMS (EI): Calc. for $C_9H_8F_8N_2O$: 312.0509. Found: 312.0515.

3.3.3. One-pot synthesis of polyfluoroalkoxylated heterocycles **6** and **8** from the ammonium iodide **1**

To a mixture of the ammonium iodide **1** (10.0 mmol), polyfluoroalcohol (11.0 mmol) and molecular sieves 4A (10.0 g) in MeCN (30 ml) was gradually added sodium hydride (11.0 mmol) at 0°C and the mixture was stirred at room temperature for 0.5 h. After the addition of a secondary amine (50.0 mmol), the mixture was heated at 70°C for 1 h with stirring. Subsequently, the amidinium salt (15 mmol) or the hydrazine (15 mmol) and a 28 wt.% methanol solution of sodium methylate (15 mmol) were added to the reaction mixture, which was stirred at room temperature or at 70°C for another 3 h. After cooling to room temperature, the mixture was treated in the same manner as described in Section 3.3.1 or Section 3.3.2 to give the corresponding products **6** or **8**. The results are summarized in Table 3.

References

- [1] D. Lloyd, H. McNab, *Angew. Chem., Int. Ed. Engl.* 15 (1976) 459.
- [2] J.T. Gupton, D.A. Krolikowski, R.H. Yu, S.W. Riesinger, J.A. Sikorski, *J. Org. Chem.* 55 (1990) 4735.
- [3] J.T. Gupton, D.A. Krolikowski, R.H. Yu, P. Vu, J.A. Sikorski, M.L. Dahl, C.R. Jones, *J. Org. Chem.* 57 (1992) 5480.
- [4] S.N. Balasubrahmanyam, B. Jeyashri, I.N.N. Namboothiri, *Tetrahedron* 50 (1994) 8127.
- [5] S.A. Petrich, F.A. Hicks, D.R. Wilkinson, J.G. Tarrant, S.M. Bruno, M. Vargas, K.N. Hosein, J.T. Gupton, J.A. Sikorski, *Tetrahedron* 51 (1995) 1575.
- [6] J.T. Gupton, J.E. Gall, S.W. Riesinger, S.Q. Smith, K.M. Bevirt, J.A. Sikorski, M.L. Dahl, Z. Arnold, *J. Heterocyclic Chem.* 28 (1991) 1281.
- [7] J.T. Gupton, S.W. Riesinger, A.S. Shah, J.E. Gall, K.M. Bevirt, *J. Org. Chem.* 56 (1991) 976.
- [8] A. Ehmann, R. Gompper, H. Hartmann, T.J.J. Muller, K. Polborn, R. Schutz, *Angew. Chem., Int. Ed. Engl.* 33 (1994) 572.
- [9] C. Payrastré, N. Obaya, Y. Madaule, J.G. Wolf, *Tetrahedron Lett.* 35 (1994) 3059.
- [10] M.R. Mazieres, V.D. Ramanenko, A.O. Gudima, C. Payrastré, M. Sanchez, J.G. Wolf, *Tetrahedron* 51 (1995) 1405.
- [11] F.A. Cotton, L.M. Daniels, S.C. Haefner, C.A. Murillo, *J. Chem. Soc. Chem. Commun.* (1996) 2507.
- [12] C. Reichardt, K. Halbritter, *Justus Liebigs Ann. Chem.* 737 (1970) 99.
- [13] C. Reichardt, K. Halbritter, *Justus Liebigs Ann. Chem.* (1975) 470.
- [14] V.I. Saloutin, Z.E. Skryabina, Y.V. Burgart, O.N. Chupakhin, M. Font-Altaba, X. Solans, M. Font-Bardia, *J. Fluorine Chem.* 69 (1994) 25.
- [15] H. Yamanaka, S. Yamashita, T. Ishihara, *Tetrahedron Lett.* 33 (1992) 357.
- [16] H. Yamanaka, T. Takekawa, K. Morita, T. Ishihara, *Tetrahedron Lett.* 37 (1996) 1829.
- [17] H. Yamanaka, S. Yamashita, T. Ishihara, *Synlett* (1993) 353.
- [18] X. Shi, T. Ishihara, H. Yamanaka, J.T. Gupton, *Tetrahedron Lett.* 36 (1995) 1527.
- [19] H. Yamanaka, H. Ganbayashi, M. Kuwabara, K. Fukunishi, M. Nomura, *Nippon Kagaku Kaishi* (1988) 1036.
- [20] H. Yamanaka, S. Yamashita, K. Fukunishi, M. Kuwabara, T. Ishihara, M. Nomura, *J. Fluorine Chem.* 52 (1991) 185.
- [21] M. Hojo, R. Masuda, E. Okada, S. Sakaguchi, H. Narumiya, K. Morimoto, *Tetrahedron Lett.* 30 (1989) 6173.
- [22] H. Yamanaka, K. Shiomi, T. Ishihara, *Tetrahedron Lett.* 36 (1995) 7267.
- [23] *Handbook of Tables for Organic Compound Identification*, compiled by Z. Rappoport, 3rd edn., CRC Press, OH, 1967, pp. 436–439.