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Reaction of β-trifluoroethoxy vinamidinium salts with carbon nucleophiles

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Abstract

β-Trifluoroethoxy vinamidinium salts **1** reacted smoothly with various types of the carbanions, generated by treatment of ketones, esters, amide and nitriles with LDA, to give the corresponding trifluoroethoxylated multifunctional dienamine derivatives **3** in moderate to good yields. On the other hand, the reaction of **1** with lithium acetylide and other carbanions derived from methyl compounds bearing sulfonyl, sulfinyl, and phosphonyl groups produced the corresponding α,β-unsaturated aldehydes **5** in good yields.

Keywords: Vinamidinium salt; Trifluoroethoxy group; Enamines; Dienamines; α,β-Unsaturated aldehydes

1. Introduction

Many kinds of enamines and dienamines have been prepared and utilized as very important building blocks in organic synthesis (for the review on enamine chemistry, see [1]) and their chemistry has been widely documented [1,2]. Recently, the fluorine-containing analogues have also attracted much attention since they could serve as the fluorinated synthons for the synthesis of various new fluorinated compounds and also for the introduction of fluorine substituents into natural products. Regarding the preparation of the fluorinated enamines and dienamines, various new methods [3–11] have been developed in addition to the classical methods based on the reactions of perfluoroalkenes [12–15] or 1*H*-perfluoroalkynes [16–19] with amines. Although the fluorine-containing enamines and dienamines carrying functional groups such as ketone, ester and nitrile are expected to be valuable building blocks, there are only a few reports on their synthesis [20–22]. Recently, we have shown that β-monofluoro [23] and β-trifluoromethyl vinamidinium salts [24] are very useful synthons for the preparation of fluorinated multifunctional dienamine derivatives by the reaction with carbon nucleophiles. In this connection, we have investigated the synthesis of trifluoroethoxylated multifunctional dienamine derivatives by the reaction of β-trifluoroethoxy vinamidinium salts with various carbanions generated from ketones, esters, amide and nitriles. We have also examined the reaction of **1** with the carbanions derived from sulfone, sulfoxide, and phosphonate containing compounds. Herein, we wish to report on the results of these studies.

Recently, trifluoroethoxylated agrochemicals and medicinal agents have also attracted great interests and have been utilized as herbicide, fungicide, antiulcerative, and antiarrhythmic reagents [25,26]. Incidentally, as of 1996, there were approximately 450 commercially available organofluorine drugs on the market, of which 85% were monofluorinated compounds and 15% were trifluoromethylated compounds [25].

2. Results and discussion

The reaction of 1,1,5,5-tetraethyl-3-(2,2,2-trifluoroethoxy)-1,5-diaza-1,3-pentadienium iodide (β-trifluoroethoxy vinamidinium salt) (**1a**) with enolate anion generated from acetophenone (**2a**) and lithium diisopropylamide (LDA) was investigated under various conditions (Scheme 1). The results are summarized in Table 1.

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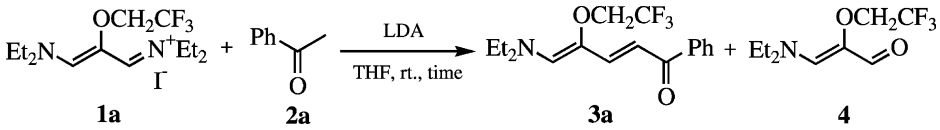


1a 2a 3a 4

Scheme 1.

Table 1
Optimization of the reaction of **1a** with **2a**

Entry	Equivalent of **2a**	Additive[a]	Time (h)	Yield[b] of **3a** (%)	Yield[b] of **4** (%)	Recoverd[c] of **1a** (%)
1	1.1	Et_3N	1	26 (26)	13 (20)	47
2	1.1	Et_3N	16	(22)	(54)	17
3	1.1[d]	none	16	56 (61)	16 (19)	11
4	1.5	Et_3N	16	50 (52)	32 (34)	10
5	2.2	Et_3N	16	86 (92)	(0)	0
6	2.2	None	16	85 (91)	(0)	0

[a] 3.0 eq. of Et_3N were used.
[b] Isolated yields. Values in parentheses are yields determined by ^{19}F NMR.
[c] Determined by ^{19}F NMR.
[d] Excess amount (2.4 eq.) of LDA were used.

Table 2
Results of reaction of **1a** with various nucleophiles **2b–e**

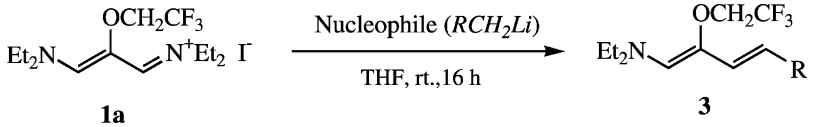
Entry[a]	Substrate ($R–CH_3$)	R of $LiCH_2R$	Yield[b] of **3** (%)
1	Ethyl acetate (**2b**)	CO_2Et	78
2	Pinacolone (**2c**)	$COBu^t$	78
3	*N,N*-Dimethyacetamide (**2d**)	$CONMe_2$	55 (81)
4	Acetonitrile (**2e**)	CN	83

[a] All reactions were performed by using 2.2 eq. of **2** and 2.4 eq. of LDA.
[b] Isolated yield. Value in parentheses is the yield determined by ^{19}F NMR.

When the salt **1a** was allowed to react with the enolate, generated from 1.1 eq. of **2a** and 1.2 eq. of LDA, in the presence of triethylamine (3.0 eq.) in tetrahydrofuran (THF) at room temperature for 1 h, an addition-deamination product, 5-(diethylamino)-1-phenyl-4-(2,2,2-trifluoroethoxy)-2,4-pentadien-1-one (**3a**) (26% yield) and 3-(diethylamino)-2-(2,2,2-trifluoroethoxy)-2-propenal (**4**) (13% yield) were obtained along with some recovered starting material **1a** (entry 1). The latter product **4** might be produced via hydrolysis of **1a** [9]. Prolongation of the reaction time (16 h) under the same conditions did not improve the yield of **3a** (entry 2). However, the employment of excess amount (2.4 eq.) of LDA gave **3a** in 56% yield (entry 3). Furthermore, an increase in the amount of the enolate dramatically changed the yield of **3a**. Thus, the employment of 2.2 eq. of the enolate gave **3a** in 86% yield with no formation of **4** as well as no recovery of **1a** (entry 5). Although triethylamine was a useful additive in the reaction of a β-fluoro vinamidinium salt with enolates in previous studies [23], the present reaction benefits (85% yield of **3a**) in the absence of triethylamine as shown in entry 6. This may suggest that the excess amounts of the enolate act as a stronger base when compared to triethylamine in the α-hydrogen abstraction of the reaction intermediate cited in Scheme 4.

We next examined the reactions of **1a** with other enolates generated from ethyl acetate (**2b**), pinacolone (**2c**) and *N,N*-dimethylacetamide (**2d**) under optimized conditions (entry 5 in Table 1) (Scheme 2) and the results are summarized in Table 2. All enolates employed smoothly reacted with **1a** to give the corresponding dienamine derivatives **3b–d** in good yields. The carbanion generated from acetonitrile (**2e**) and LDA also reacted with **1a** to afford the desired product **3e** in 83% yield.

The dienamine derivatives **3** were obtained as single geometrical isomers and their structures were determined by ^1H NMR. The coupling constants between H_a and H_b of all dienamine derivatives **3** were observed in the range of 14.4–15.5 Hz, which indicated the *trans* geometry [27] (Fig. 1). Additionally, the NOEs between H_b and H_c, and between methylene protons of the diethylamino group and the trifluoroethoxy groups were observed in the NOESY spectra of **3a**. This observation confirmed the *transoid* structure between the two double bonds as well as the (*Z*)-configuration at the C4–C5 double bond. An NOE was also observed between the *ortho* protons of the phenyl group and H_a but not H_b. This strongly suggests that the carbonyl group has the *cisoid* relationship towards the C2–C3 double bond. The (2*E*,4*Z*)-configuration of the other dienamine derivatives **3** was based on a comparison of the chemical shifts (δ −74.65 to −74.85 ppm in ^{19}F NMR spectra with $CFCl_3$ as internal standard) of the trifluoromethyl group with that (−74.66 ppm) of **3a**. The current results obtained for the structure ((2*E*,4*Z*)-configuration) of the dienamine derivatives **3** showed a sharp contrast with previous structural assignments ((2*E*,4*Z*)-configuration) of



1a 3

Scheme 2.

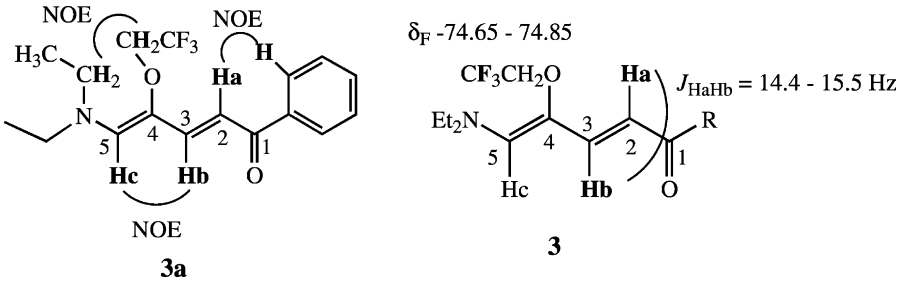
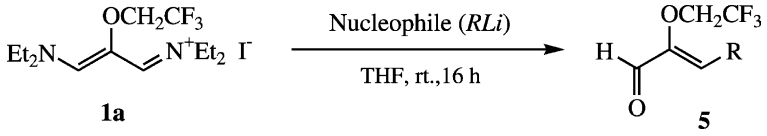


Fig. 1. NMR spectra data of dienamine derivatives **3** and **3a**.



Scheme 3.

the dienamine derivatives obtained in the reaction of the same enolates with 1,1,5,5-tetramethyl-3-(trifluoromethyl)-1,3-pentadienium chloride (β-trifluoromethyl vinamidinium salt) [24]. This difference in the stereochemistry at the C4–C5 double bond may be rationalized based on a negligible steric repulsion between the trifluoroethoxy and the diethylamino group relative to a strong one between the trifluoromethyl and the dimethylamino group. Although the trifluoroethoxy group is more bulky than the trifluoromethyl group, it is also more flexible and can avoid the undesirable steric repulsion.

Interestingly, the reaction of the salt **1a** with the carbanions from methyl phenyl sulfone (**2f**), methyl phenyl sulfoxide (**2g**) and diethyl methylphosphonate (**2h**), and with the enolate generated from propiophenone (**2i**) gave α,β-unsaturated aldehydes **5f–i** (Scheme 3 and Table 3) as the product. These reactions took place very smoothly and ^{19}F NMR spectra of the reaction mixtures showed the formation of a single product. After a standard aqueous workup followed by column chromatography, a single geometrical isomer of the corresponding aldehydes **4f–i** were obtained in moderate to good yields from substrates **2f–h** (entries 1–3). Although aqueous workup of the reaction mixture of **2i** resulted in many unidentified products, column chromatography before aqueous workup gave the aldehyde **5i** in 83% yield with a 30/70 of *E*/*Z*-isomer ratio. The reaction with similar enolates from α-alkylated carbonyl compounds such as 2-pentanone and cyclohexanone similarly proceeded to form a single product, which converted to complex mixtures during aqueous workup or column chromatography.

Table 3
Results of reaction of **1a** with various nucleophiles **2f–j**

Entry[a]	Substrate (R–H)	R of LiR	Yield[b] of **5** (%)
1	Methyl phenyl sulfone (**2f**)	CH_2SO_2Ph	(78)
2	Methyl phenyl sulfoxide (**2g**)	$CH_2S(O)Ph$	49
3	Diethyl methylphosphonate (**2h**)	$CH_2P(O)(OEt)_2$	67
4	Propiophenone (**2i**)	$CH(CH_3)COPh$	83[c]
5	1-Octyne (**2j**)	$C{\equiv}(CH_2)_5CH_3$	83[c]

[a] All reactions were performed by using 2.2 eq. of **2** and 2.4 eq. of LDA.

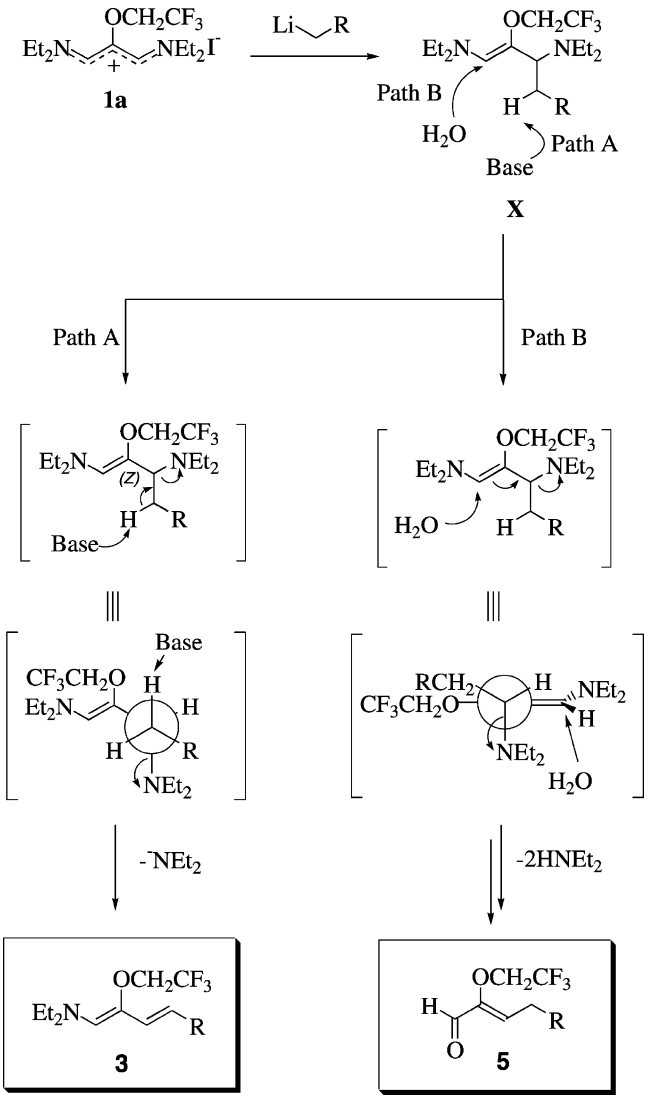
[b] Isolated yield. Value in parentheses is the yield determined by ^{19}F NMR.

[c] Combined yield of the *E*- and *Z*-isomers.

The lithium carbanion generated from 1-octyne (**2j**) similarly reacted with **1a** to give a mixture of the *E*- and *Z*-isomers (22/78) of α,β-unsaturated aldehyde **5j**in 83% yield after aqueous workup and column chromatography.

A possible reaction mechanism for the formation of **3** and **5** is shown in Scheme 4. The carbanion presumably attacks on the α carbon of the vinamidinium salt (**1a**) to form a tetrahedral intermediate (**X**). When the α hydrogen of **X** is strongly acidic or sterically less hindered, dediethylamination occurs via assistance of base (carbanion) to give the dienamine derivatives **3** (Path A). The selective formation of the 2*E*-isomer of **3** may be explained by anti elimination of diethylamine from the most stable conformer of the intermediate **X**. On the other hand, when the α hydrogen is weakly acidic and/or sterically hindered, the base cannot attack it and the intermediate **X** does not undergo elimination of the diethylamino group. Consequently, aqueous workup results in the elimination of diethylamino group to produce the aldehydes **5** via the formation of the *N*,*O*-acetal (Path B).

We have also examined the reaction of the salt **1** with enolates generated from 1,3-dicarbonyl compounds and sodium hydride (NaH). Thus, the reaction with the enolate from diethyl malonate (**2k**) (1.1 eq.) and NaH (1.2 eq.) in the presence of triethylamine (3.0 eq.) in THF at room temperature for 3 h gave the expected dienamino ester, 5-diethylamino-2-ethoxycarbonyl-4-trifluoroethoxy-2,4-pentadienoate (**6k**), only in 21% yield with recovery of **1** (13%).



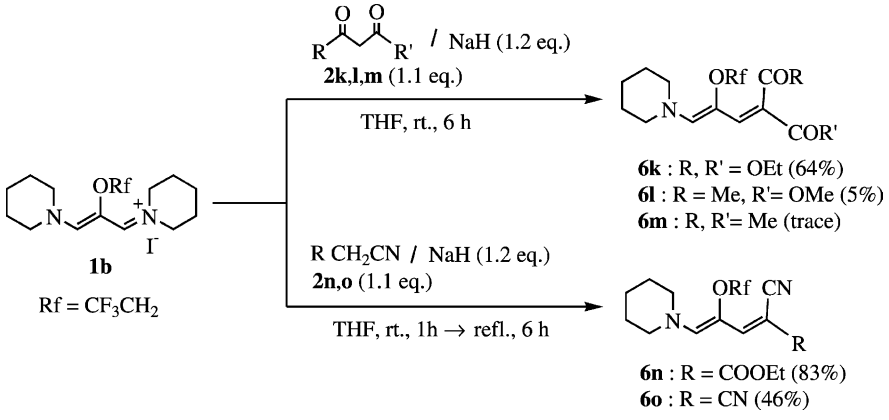
Scheme 4.

Even if the reactions were carried out using 2.2–4.4 eq. of **2k** at room to refluxing temperatures for 1–16 h, satisfactory results were not obtained. However, when the β-trifluoroethoxy vinamidinium salt **1b** having the piperidino group instead of the diethylamino group was employed, the reaction smoothly took place to give the product **6k** in moderate yield. Thus, the reaction of **1b** with **2k** (1.1 eq.) and NaH (1.2 eq.) at room temperature for 1 h and then at refluxing temperature for 6 h afforded the dienamino ester **6k** in 64% yield (Scheme 5). The results may be explained by the influence of the substituent at nitrogen of the vinamidinium salt; the nucleophile can more easily approach the α carbon of **1b** rather than **1a** because the cyclic piperidino group is smaller and less bulky than the diethylamino group. The use of 2.2 eq. of **2k** under the same conditions gave a mixture of many unidentified products.

Although the reactions with enolates from methyl acetoacetate (**2l**) and acetylacetone (**2m**) were similarly conducted under the same conditions, the corresponding dienamino esters were obtained in only trace amounts. However, the reaction with the carbanion from ethyl cyanoacetate (**2n**) took place cleanly to produce ethyl (2*E*,4*Z*)-2-cyano-5-piperidino-4-(2,2,2-trifluoroethoxy)-2,4-pentadienoate (**6n**) in 83% yield. The carbanion from malononitrile (**2o**) also participated in the reaction with **1b** to give (4*Z*)-2-cyano-5-piperidino-4-(2,2,2-trifluoroethoxy)-2,4-pentadienenitrile (**6o**) in 46% yield (Scheme 5).

3. Conclusion

The present study demonstrates that β-trifluoroethoxy vinamidinium salts **1** are very useful synthons for the synthesis of the trifluoroethoxylated multifunctional dienamine derivatives **3** by their reaction with carbon mucleophiles generated from esters, ketones, amide and nitriles. It was also found that vinamidinium salt (**1**) nicely participated in reactions with the carbanions derived from sulfone, sulfoxide, phosphonate and acetylenic compounds to give α,β-unsaturated aldehydes **5**, which are extremely useful in organic synthesis. This procedure should be widely applicable to the synthesis of a variety of polyfluoroalkoxylated dienamine derivatives and α,β-unsaturated aldehydes by using the vinamidinium salts containing other polyfluoroalkoxy groups [28].



Scheme 5.

4. Experimental

4.1. Measurement and materials

Infrared spectra (IR) were measured in a liquid film or KBr disk method with a Shimadzu FTIR-8200PC spectrophotometer. ^{1}H NMR spectra were obtained with a General Electric QE-300 (300 MHz) spectrometer in a chloroform-d ($CDCl_3$) solution with tetramethylsilane (TMS) as an internal reference. ^{13}C NMR spectra and NOESY spectra were obtained with a Bruker DRX500 (126 MHz) spectrometer in a chloroform-d ($CDCl_3$) solution. A Japan Electronics JNM EX90 (84.10 MHz) spectrometer was used to measure ^{19}F NMR spectra in $CDCl_3$ with trichlorofluoromethane (CCl_3F) as an internal reference. High resolution mass spectra (HRMS) were taken on a Hitachi M-80B mass spectrometer operating at an ionization potential of 70 eV. Melting points were obtained on a Mettler FP5 or Mitamura melting point determination apparatus and are uncorrected.

All chemicals are of reagent grade and, if necessary, were purified by a conventional manner before use. Tetrahydrofuran (THF) was distilled with sodium benzophenone ketyl and stored under argon. All reactions were carried out under an atmosphere of argon. Yields based on ^{19}F NMR were calculated by peak area ratio of the sample to benzotrifluoride (BTF) as an internal reference. Two kinds of vinamidinium salts (**1a** and **b**) were prepared according to the method previously reported [28].

4.2. Typical procedure for the reaction of the salt *1a* with carbon nucleophiles

To a solution of diisopropylamine (0.242 g, 2.4 mmol) in THF (3.0 ml) was gradually added *n*-butyllithium in hexane (1.6 M, 1.50 ml, 2.4 mmol) and then the mixture was stirred at 0 °C for 0.5 h under an argon atmosphere. To the resulting solution was gradually added acetophenone (0.092 g, 2.2 mmol) and then the mixture was stirred at 0 °C for 0.5 h. To this solution was gradually added β-trifluoroethoxy vinamidinium salt (**1a**) (0.408 g, 1.0 mmol) and then the mixture was stirred at room temperature for 16 h. Ice water (30 ml) was added to the reaction mixture and extracted with dichloromethane (20 ml × 3). The organic layers were combined, washed with brine (30 ml) and dried over anhydrous sodium sulfate. After removal of the solvents, the residue was purified by silica gel column chromatography to give the product **3a** (0.278 g, 0.850 mmol, 85% yield).

The reaction mixtures from methyl phenyl sulfone (**2f**), methyl phenyl suloxide (**2g**), methyl diethylphosphonate (**2h**), propiophenone (**2i**) and 1-octyne (**2j**) were passed through a short silica gel column. The filtrates were concentrated in *vacuo* to give the crude materials, which were purified by silica gel column chromatography to isolate the products (**4f–j**).

4.2.1. (2E,4Z)-5-Diethylamino-1-phenyl-4-(2,2,2-trifluoroethoxy)-2,4-pentadien-1-one (*3a*)

mp 79–81 °C; ^{1}H NMR ($CDCl_3$): δ 1.22 (t, $J = 7.2$ Hz, 6H), 3.38 (q, $J = 7.2$ Hz, 4H), 4.11 (q, $J = 8.6$ Hz, 2H), 6.12 (s, 1H), 6.67 (d, $J = 14.4$ Hz, 1H), 7.28 (d, $J = 14.4$ Hz, 1H), 7.46 (m, 3H), 7.96 (m, 2H); ^{19}F NMR ($CDCl_3$): δ −74.66 (t, $J = 8.6$ Hz, 3F); IR (KBr): 1643 (m), 1520 (vs), 1420 (s), 1281 (w), 1254 (m), 1223 (s), 1173 (s), 1153 (s), 1123 (w), 1080 (w), 1049 (w) cm^{-1}; MS (EI) *m/z* (rel. intensity): 327 (M^+, 5), 244 (7), 229 (17), 228 (100), 105 (11); HRMS (EI) Calcd. for $C_{17}H_{20}F_3NO_2$: 327.1447, Found 327.1451; Anal. Calcd. for C, 62.38; H, 6.16; N, 4.28. Found C, 62.24; H, 6.13; N, 4.23.

4.2.2. Ethyl (2E,4Z)-5-diethylamino-4-(2,2,2-trifluoroethoxy)-2,4-pentadienoate (*3b*)

^{1}H NMR ($CDCl_3$): δ 1.17 (t, $J = 7.2$ Hz, 6H), 1.28 (t, $J = 7.2$ Hz, 3H), 3.31 (q, $J = 7.2$ Hz, 4H), 4.04 (q, $J = 8.6$ Hz, 2H), 4.17 (q, $J = 7.2$ Hz, 2H), 5.45 (d, $J = 14.7$ Hz,1H), 5.90 (s, 1H), 6.99 (d, $J = 14.7$ Hz, 1H); 19F NMR ($CDCl_3$): δ −74.65 (t, $J = 8.6$ Hz, 3F); IR (neat): 2978 (w), 1736 (s), 1670 (m), 1628 (w), 1585 (s), 1420 (w), 1369 (w), 1281 (vs), 1165 (vs), 1099 (w), 1076 (w) cm^{-1}; MS (EI) *m/z* (rel. intensity): 295 (M^+, 68), 266 (8), 250 (22), 222 (8), 213 (13), 212 (100), 206 (5); HRMS (EI) Calcd. for $C_{13}H_{20}F_3NO_3$: 295.1395, Found 295.1398.

4.2.3. (1Z,3E)-1-Diethylamino-6,6-dimethyl-2-(2,2,2-trifluoroethoxy)-1,3-heptadien-5-one (*3c*)

mp 58–59 °C; ^{1}H NMR ($CDCl_3$): δ 1.17 (s, 9H), 1.18 (t, $J = 7.1$ Hz, 6H), 3.33 (q, $J = 7.1$ Hz, 4H), 4.02 (q, $J = 8.6$ Hz, 2H), 5.98 (s, 1H), 6.23 (d, $J = 14.4$ Hz,1H), 7.06 (d, $J = 14.4$ Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −74.83 (t, $J = 8.6$ Hz, 3F); IR (neat): 2966 (w), 1655 (m), 1632 (w), 1543 (s), 1416 (s), 1362 (w), 1277 (m), 1258 (m), 1161 (m), 1123 (w), 1072 (m), 988 (w), 968 (w) cm^{-1}; MS (EI) *m/z* (rel. intensity): 307 (M^+, 13), 250 (26), 224 (13), 222 (26), 209 (14), 208 (100), 194 (7); HRMS (EI) Calcd. for $C_{15}H_{24}F_3NO_2$: 307.1759, Found 307.1759.

4.2.4. (2E,4Z)-N,N-Dimethyl-5-diethylamino-4-(2,2,2-trifluoroethoxy)-2,4-pentadienamide (*3d*)

^{1}H NMR ($CDCl_3$): δ 1.16 (t, $J = 7.1$ Hz, 6H), 3.04 (m, 6H), 3.28 (q, $J = 7.1$ Hz, 4H), 4.03 (q, $J = 8.5$ Hz, 2H), 5.85 (s, 1H), 5.81 (d, $J = 14.4$ Hz, 1H), 7.00 (d, $J = 14.4$ Hz,1H); ^{19}F NMR ($CDCl_3$): δ −74.85 (t, $J = 8.5$ Hz, 3F). The measurement of MS and/or elemental analysis of **3d** were not taken because of its instability in neat state.

4.2.5. (2E,4Z)-5-Diethylamino-4-(2,2,2-trifluoroethoxy)-2,4-pentadiene-nitrile (*3e*)

^{1}H NMR ($CDCl_3$): δ 1.18 (t, $J = 7.2$ Hz, 6H), 3.32 (q, $J = 7.2$ Hz, 4H), 3.98 (q, $J = 8.5$ Hz, 2H), 4.78 (d, $J = 15.5$ Hz, 1H), 5.88 (s, 1H), 6.59 (d, $J = 15.5$ Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −74.75 (t, $J = 8.5$ Hz, 3F); IR (neat):

2978 (w), 2199 (m), 1632 (vs), 1582 (s), 1454 (w), 1423 (m), 1381 (w), 1277 (s), 1169 (s), 1080 (w) cm^{-1}; MS (EI) *m/z* (rel. intensity): 248 (M^+, 59), 233 (5), 116 (11), 165 (100), 137 (4), 121 (5), 109 (4); HRMS (EI) Calcd. for $C_{11}H_{15}F_3N_2O$: 248.1136, Found 248.1137.

*4.2.6. (Z)-4-Phenylsulfonyl-2-(2,2,2-trifluoroethoxy)-2-butenal (**5f**)*

^{1}H NMR ($CDCl_3$): δ 4.17 (d, $J = 7.8$ Hz, 2H), 4.31 (q, $J = 8.4$ Hz, 2H), 6.09 (t, $J = 7.8$ Hz, 1H), 7.50–7.72 (m, 3H), 7.90 (m, 2H), 9.28 (s, 1H); ^{19}F NMR ($CDCl_3$): δ −75.50 (t, $J = 8.4$ Hz, 3F). The measurement of MS and/or elemental analysis of **5f** were not taken because of being not purely isolated.

*4.2.7. (Z)-4-Phenylsulfinyl-2-(2,2,2-trifluoroethoxy)-2-butenal (**5g**)*

^{1}H NMR ($CDCl_3$): δ 3.75 (dd, $J = 13.2$, 8.4 Hz, 1H), 3.98 (dd, $J = 13.2$, 7.5 Hz, 1H), 4.21 (dq, $J = 12.6$, 8.4 Hz, 1H), 4.43 (dq, $J = 12.6$, 8.4 Hz, 1H), 6.07 (dd, $J = 8.4$, 7.5 Hz, 1H), 7.50–7.64 (m, 5H), 9.23 (s, 1H); ^{19}F NMR ($CDCl_3$): δ −75.33 (t, $J = 8.4$ Hz, 3F); IR (neat): 1963 (s), 1447 (w), 1354 (w), 1277 (s), 1227 (w), 1165 (s), 1088 (m), 1045 (w), 968 (w), 748 (w), 691 (w) cm^{-1}; MS (CI) *m/z* (rel. intensity): 293 ($M^+ + H$, 71), 251 (49), 235 (100), 219 (34).

*4.2.8. (Z)-4-Diethyl phosphono-2-(2,2,2-trifluoroethoxy)-2-butenal (**5h**)*

^{1}H NMR ($CDCl_3$): δ 1.34 (t, $J = 6.9$ Hz, 6H), 2.96 (dd, $J = 23.2$, 8.1 Hz, 2H), 4.13 (q, $J = 6.9$ Hz, 2H), 4.15 (q, $J = 6.9$ Hz, 2H), 4.52 (q, $J = 8.7$ Hz, 2H), 6.11 (td, $J = 8.1$, 7.5 Hz, 1H), 9.28 (s, 1H); ^{19}F NMR ($CDCl_3$): δ −75.46 (t, $J = 8.7$ Hz, 3F); IR (neat): 2986 (w), 1693 (s), 1647 (w), 1396 (w), 1358 (w), 1277 (s), 1165 (s), 1026 (s), 968 (s), 806 (w) cm^{-1}; MS (CI) *m/z* (rel. intensity): 305 ($M^+ + H$, 100), 291 (19), 229 (13).

*4.2.9. (Z)-4-Methyl-5-oxo-5-phenyl-2-(2,2,2-trifluoroethoxy)-2-pentenal (**Z-5i**)*

^{1}H NMR ($CDCl_3$): δ 1.40 (d, $J = 7.2$ Hz, 3H), 4.56 (q, $J = 8.4$ Hz, 1H), 4.57 (q, $J = 8.4$ Hz, 1H), 4.85 (dq, $J = 9.9$, 7.2 Hz, 1H), 6.28 (d, $J = 9.9$ Hz, 1H), 7.99 (m, 5H), 9.24 (s, 1H); ^{19}F NMR ($CDCl_3$): δ −74.25 (t, $J = 8.4$ Hz, 3F). GCMS (EI) *m/z* (rel. intensity): 286 (M^+, 5), 181 (5), 105 (100), 77 (95).

*4.2.10. (E)-4-Methyl-5-oxo-5-phenyl-2-(2,2,2-trifluoroethoxy)-2-pentenal (**E-5i**)*

^{1}H NMR ($CDCl_3$): δ 1.38 (d, $J = 7.8$ Hz, 3H), 4.17 (q, $J = 8.1$ Hz, 1H), 4.18 (q, $J = 8.1$ Hz, 1H), 5.32 (dq, $J = 9.9$, 7.8 Hz, 1H), 5.76 (dd, $J = 9.9$, 2.7 Hz, 1H), 7.45–7.63 (m, 5H), 9.66 (d, $J = 2.7$ Hz, 1H); ^{19}F NMR ($CDCl_3$): δ −75.38 (t, $J = 8.1$ Hz, 3F). GCMS (EI) *m/z* (rel. intensity): 286 (M^+, 5), 267 (7), 181 (5), 128 (10), 105 (100), 77 (95).

*4.2.11. (Z)-2-(2,2,2-Trifluoroethoxy)-2-undecen-4-ynal (**Z-5j**)*

^{1}H NMR ($CDCl_3$): δ 0.90 (m, 3H), 1.26–1.65 (m, 8H), 2.47 (td, $J = 6.5$, 2.4 Hz, 2H), 4.66 (q, $J = 8.3$ Hz, 2H), 5.90 (t, $J = 2.4$ Hz, 1H), 9.19 (s, 1H); ^{19}F NMR ($CDCl_3$): δ −74.41 (t, $J = 8.3$ Hz, 3F); IR (neat): 2936 (m), 2826 (w), 2214 (w), 1693 (s), 1609 (w), 1454 (w), 1408 (w), 1362 (m), 1277 (m), 1161 (s), 1088 (m), 968 (m) cm^{-1}; MS (EI) *m/z* (rel. intensity): 262 (M^+, 10), 234 (12), 233 (81), 231 (11), 215 (10), 205 (25); HRMS (EI) Calcd. for $C_{13}H_{17}F_3O_2$: 262.1180, Found 262.1137.

*4.2.12. (E)-2-(2,2,2-Trifluoroethoxy)-2-undecen-4-ynal (**E-5j**)*

^{1}H NMR ($CDCl_3$): δ 0.90 (m, 3H), 1.25–1.62 (m, 8H), 2.40 (td, $J = 7.1$, 2.6 Hz, 2H), 4.27 (q, $J = 8.1$ Hz, 2H), 6.10 (t, $J = 2.6$ Hz, 1H), 9.97 (s, 1H); ^{19}F NMR ($CDCl_3$): δ −74.44 (t, $J = 8.1$ Hz, 3F); MS (EI) *m/z* (rel. intensity): 262 (M^+, 14), 233 (11), 218 (23), 206 (14), 205 (48), 193 (12); HRMS (EI) Calcd. for $C_{13}H_{17}F_3O_2$: 262.1180, Found 262.1138.

*4.3. Typical procedure for the reaction of the salt **1b** with 1,3-dicarbonyl and cyano compounds*

To a solution of the sodium hydride (0.029 g, 1.2 mmol) in THF (3.0 ml) was gradually added diethyl malonate (**2k**) (0.176, 1.1 mmol) and then the mixture was stirred at 0 °C for 0.5 h under an argon atmosphere. To the above solution was gradually added vinamidinium salt (**1b**) (0.432 g, 1.0 mmol) and then the mixture was stirred at room temperature for 6 h. Ice water (30 ml) was added to the reaction mixture and extracted with dichloromethane (20 ml × 3). The organic layers were combined, washed with brine (30 ml), dried over anhydrous sodium sulfate and concentrated in *vacuo*. The crude materials were purified by silica gel column chromatography to give ethyl 2-ethoxycarbonyl-5-piperidino-4-(2,2,2-trifluoroethoxy)-2,4-pentadienoate (**6k**) (0.243 g, 64% yield).

*4.3.1. Ethyl (4Z)-2-ethoxycarbonyl-5-piperidino-4-(2,2,2-trifluoroethoxy)-2, 4-pentadienoate (**6k**)*

^{1}H NMR ($CDCl_3$): δ 1.26 (t, $J = 7.1$ Hz, 3H), 1.31 (t, $J = 7.1$ Hz, 3H), 1.63 (m, 6H), 3.47 (m, 4H), 3.97 (q, $J = 8.7$ Hz, 2H), 4.19 (q, $J = 7.1$ Hz, 2H), 4.27 (q, $J = 7.1$ Hz, 2H), 6.09 (s, 1H), 6.92 (s, 1H); ^{19}F NMR ($CDCl_3$): δ –73.83 (t, $J = 8.7$ Hz, 3F); IR (neat): 2982 (w), 2939 (m), 2858 (w), 1732 (s), 1701 (s), 1628 (s), 1574 (vs), 1450 (s), 1427 (s), 1396 (m), 1369 (m), 1273 (s), 1246 (vs), 1111 (s), 1065 (m), 1030 (m) cm^{-1}; MS (EI) *m/z* (rel. intensity): 379 (M^+, 55), 334 (44), 297 (17), 296 (100), 256 (18), 251 (13); HRMS (EI) Calcd. for $C_{17}H_{24}F_3NO_5$: 379.1606, Found 379.1609.

*4.3.2. Ethyl (2E,4Z)-2-cyano-5-piperidino-4-(2,2, 2-trifluoroethoxy)-2,4-pentadienoate (**6n**)*

mp 151–152 °C; ^{1}H NMR ($CDCl_3$): δ 1.32 (t, $J = 7.2$ Hz, 3H), 1.70 (m, 6H), 3.67 (m, 4H), 4.23 (q, $J = 8.9$ Hz, 2H), 4.25 (q, $J = 7.2$ Hz, 2H), 6.47 (s, 1H), 7.29 (s, 1H); ^{19}F NMR ($CDCl_3$): δ −73.60 (t, $J = 8.9$ Hz, 3F); IR (KBr): 2203 (w), 1690 (m), 1632 (w), 1539 (s), 1450 (m), 1369 (w), 1281 (m), 1250 (s), 1196 (s), 1153 (m), 1103 (w), 1065 (w), 1026 (w) cm^{-1}; MS (EI) *m/z* (rel. intensity): 332 (M^+, 39), 287 (26), 203 (12), 162 (21); HRMS (EI) Calcd. for $C_{15}H_{19}F_3N_2O_3$: 332.1348, Found 332.1341.

*4.3.3. (4Z)-2-Cyano-5-piperidino-4-(2,2, 2-trifluoroethoxy)-2,4-pentadienenitrile (**6o**)*

mp 97–98 °C; ^{1}H NMR ($CDCl_3$): δ 1.72 (m, 6H), 3.69 (m, 4H), 4.18 (q, $J = 8.7$ Hz, 2H), 6.54 (s, 1H), 6.67 (s, 1H); ^{19}F NMR ($CDCl_3$): δ −73.42 (t, $J = 8.7$ Hz, 3F); IR (KBr): 2203 (s), 1632 (s), 1543 (vs), 1458 (m), 1369 (w), 1292 (s), 1261 (s), 1207 (m), 1157 (s), 1107 (w), 1053 (w), 972 (w), 910 (w) cm^{-1}; MS (EI) *m/z* (rel. intensity): 285 (M^+, 37), 203 (13), 202 (100), 167 (17), 162 (16); HRMS (EI) Calcd. for $C_{13}H_{14}F_3N_3O$: 285.1089, Found 285.1092.

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