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The reaction of 2-fluoroalkyl-1-iodoethylenes with arylamines: a facile method for the synthesis of fluoroalkylated quinolines and enaminoketones

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Abstract—The reaction of 2-fluoroalkyl-1-iodoethylenes with arylamines (**1**) and the subsequent acid promoted transformation of the products were described. In the presence of $ZnCl_2$ and triethylamine, **1** reacted readily with various *p*-substituted anilines in HMPA under a vacuum of 60–70 mmHg to give the corresponding enaminoaldehydes (**2**) as a mixture of *E*- and *Z*-isomers. Cyclization of **2**, without further purification in refluxing toluene, catalyzed by strong acids such as *p*-toluene sulfonic acid and trifluoromethanesulfonic acid gave 2-fluoroalkylquinolines (**3**) in good yields, while fluoroalkylated enaminoketones (**4**) were obtained predominantly when **2** was treated with acids in aqueous THF solution. A possible mechanism was proposed for the formation of **3** and **4**.

1. Introduction

Recently fluorinated compounds have been of great interest to both synthetic and medicinal chemists due to their unique physical and biological properties imparted by fluorine.[1] Among these compounds, fluorinated quinolines are the focus of considerable research and some of them have found applications in medicinal and pharmaceutical fields. For example, mefloquine ((2,8-bis(trifluoromethyl)-4-quinolinyl)(2-piperidinyl) methanol) has been used as highly effective antimalarial drug.[2] Therefore many methods have been developed for the preparation of fluoroalkylated quinolines. The traditional methods comprise two main approaches, namely, fluorination of suitable functional groups, such as $-CX_3$ (X = Cl, Br)[3] and $-CO_2H$,[4] and direct introduction of fluoroalkyl group by the reaction of fluoroalkyl iodides and haloquinolines in the presence of copper powder.[5] Recently much attention was paid to the synthesis of these fluorinated compounds by means of fluorine-containing building blocks. Many fluorinated precursors such as fluorine-containing enaminoketones,[6] *N*-arylimines,[7] propynoic acid esters,[8] α-fluoroalkyl aldehydes[9] and α-fluoroalkyl esters[10] have been used to synthesize 2-fluoroalkylquinolines. However, these fluorinated precursors are not easily available and the yields of some reactions are low. Herein we report a facile synthesis of 2-fluoroalkylquinolines and fluorinated enaminoketones from 2-fluoroalkyl-1-iodoethylenes.

2-Fluoroalkyl-1-iodoethylene (**1**), easily prepared from the reaction of fluoroalkyl iodides and acetylene,[11] are versatile fluorine-containing precursors. They have been reported to react with various nucleophilic reagents, and many fluoroalkylated heterocyclic compounds such as pyrazoles,[12] isoxazoles,[13] pyrimidines,[14] indolizines[15] and 1,4-diazepines[16] were prepared from these reactions. In the continuation of our study on their applications in the synthesis of fluorine-containing compounds, it was found that 2-fluoroalkylquinolines or fluoroalkylated enaminoketones could be conveniently synthesized in good yields from the reaction of **1** and substituted anilines under different conditions.

2. Results and discussion

In the presence of excess Et_3N, the reaction of 1-iodo-3,3,4,4,5,5,6,6,6-nonafluorohexene (**1a**) and *p*-methoxy aniline occurred at 80 °C in DMF (monitored by TLC or ^{19}F NMR). After workup a new compound was obtained. The spectral data showed that it was a mixture of *E*- and *Z*-isomer of 3-heptafluoropropyl-3-enaminoaldehyde (**2aa**). Treatment of **2aa** with polyphosphoric acid (PPA) at 170 °C

Keywords: 2-Fluoroalkyl-1-iodoethylene; Aniline; Fluoroalkylated quinoline; Fluoroalkylated enaminoketone; Acid.
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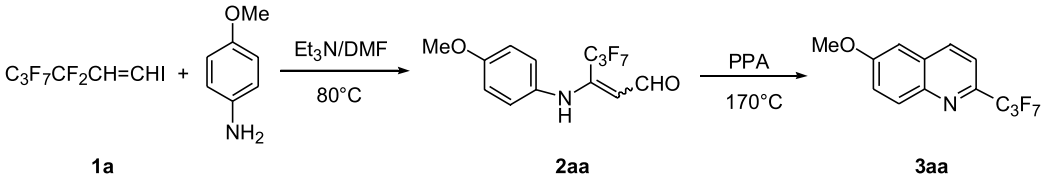


Scheme 1.

gave the corresponding cyclization product, 2-heptafluoropropyl-6-methoxyquinoline (**3aa**) (Scheme 1). The structure of **3aa** was characterized by its spectral data and further confirmed by the X-ray crystallography of its analogue, 2-(1,1,2,2,3,3-hexafluoro-3-chloropropyl)-6-methylquinoline (**3bb**) (Fig. 1).

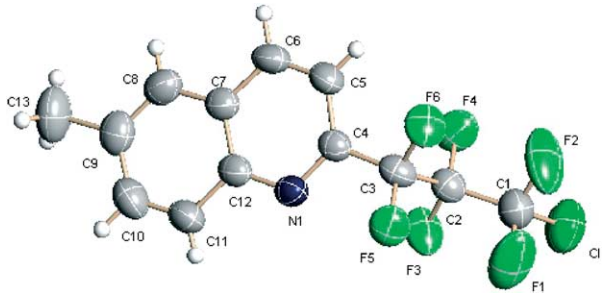


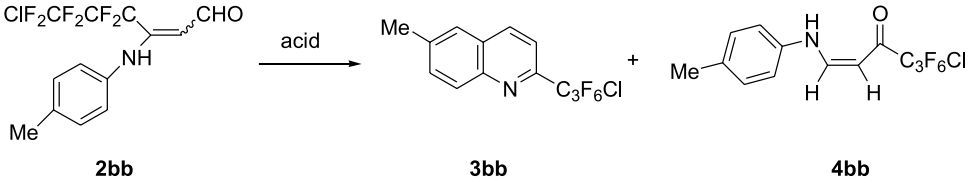
Figure 1. X-ray crystallographic structure of **3bb**.

Obviously, an acid promoted cyclization reaction was involved in the second step. In order to simplify the reaction and improve the yields of **3**, other acids such as *p*-toluene sulfonic acid, trifluoromethanesulfonic acid and concentrated hydrochloric acid were tested. It was found that the cyclization reaction of **2bb** took place readily in toluene at 120 °C in the presence of catalytic amount of TsOH or CF_3SO_3H (about 10 mol% based on **1**) to give compound **3bb** in nearly quantitative yields. However, a by-product, fluoroalkylated enaminoketone (**4bb**), was obtained in addition to the expected product **3bb** when concentrated hydrochloride acid was used in the reaction. It was hypothesized that the formation of **4bb** was attributed to the water in concentrated hydrochloric acid. Thus, 5% hydrochloric acid was tested and the expected results were obtained: **4bb** was formed as the major product. As shown in Table 1, solvent had distinct effect on the reaction and the best result was obtained in THF, as **4bb** being formed in almost quantitative yield when THF was used as the solvent (entry 4). The same result was obtained with TsOH or CF_3SO_3H when the reaction was carried out in aqueous THF solution (entries 8 and 9), confirming that water was essential for the formation of compound **4**.

A possible mechanism for the formation of **3** and **4** was proposed as shown in Scheme 2. Nucleophilic addition of the amino group in anilines to **1** followed by the elimination of a HI gave intermediate **A**, which eliminated a HF in the presence of base to afford intermediate **B**. Nucleophilic substitution of **B** by another aniline resulted in the formation of intermediate **C**. Hydrolysis of **C** gave the corresponding aldehyde **2**, which underwent cyclization promoted by strong acids to give **3**.[17] While intermediate **D** was formed from **2** in the presence of acid and water, an aniline was released at the same time. Similar transformation has been reported in the literature.[18] Subsequent reaction of **D** with aniline gave compound **4**. As a proof, intermediate **C** (Ar= 4-$MeOC_6H_4$, R_f=C_3F_7) was isolated from the reaction mixture and characterized by its spectral data.

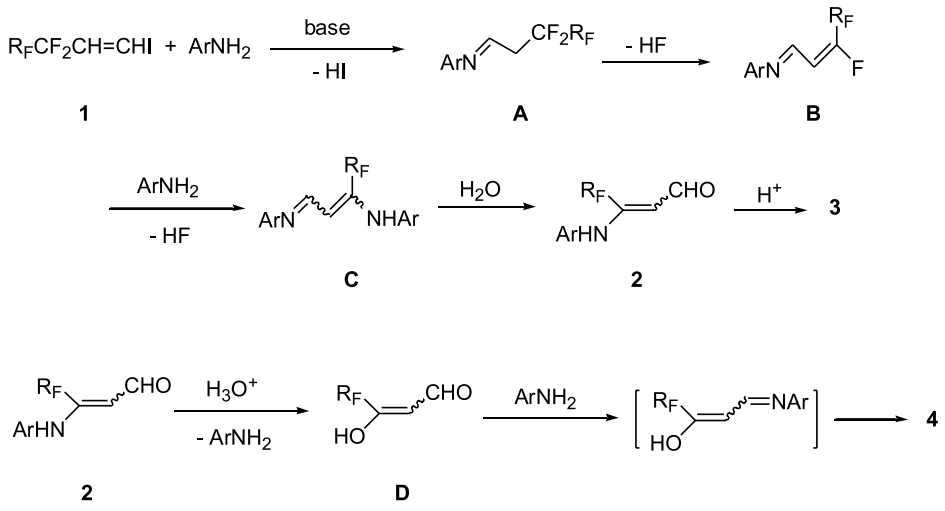
From the above results, it is very convenient to make fluoroalkylated quinolines and enaminoketones selectively from **1** by the two-step reaction using different conditions, but yields of the first step were unsatisfactory. Therefore, the conditions of the first step were optimized using the reaction of *p*-methoxyaniline with **1a** as a model reaction. It was found that in the presence of equal mole of $ZnCl_2$ and excess Et_3N, the reaction proceeded smoothly in HMPA under a vacuum of 60–70 mmHg to give **2aa** in high yield. Without purification, **2aa** was treated with TsOH directly in

Table 1. The acid promoted reaction of **2bb**



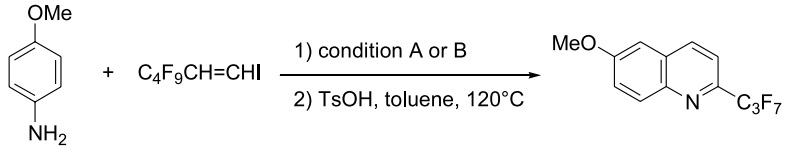
Entry	Acid	Solvent	Temperature (°C)	Time (h)	**3bb** (%)[a]	**4bb** (%)[a]
1	PPA	—	170	3	>98	—
2	TsOH	Toluene	120	3	>99	—
3	HCl(conc)	Toluene	120	4	85	15
4	5% HCl	THF	70	1	—	>99
5	5% HCl	CH_2Cl_2	60	6	—	Trace
6	5% HCl	EtOH (95%)	70	1	33	67
7	TsOH	THF/H_2O	70	2	—	>99
8	CF_3SO_3H	THF/H_2O	70	2	—	>99

[a] Determined by ^{19}F NMR.



Scheme 2.

Table 2. The reaction of **1a** with *p*-methoxyaniline under different conditions



1a **3aa**

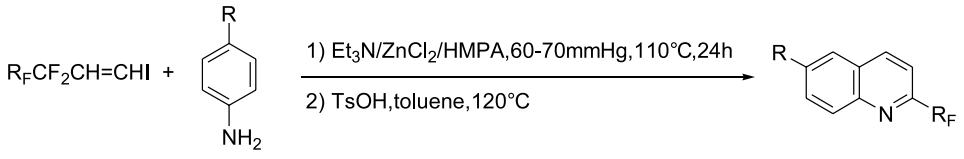
Entry	Condition[a]	Temperature (°C)[b]	Time (h)[b]	Yield (%)[c]
1	A	80	24	58
2	A	110	24	61
3	A	80	48	61
4	B	110	24	92

[a] Condition A: Et_3N/DMF, △; condition B: $Et_3N/ZnCl_2$/HMPA, 60–70 mmHg, △.
[b] Conditions for the first step.
[c] Isolated yields based on **1a**.

toluene and **3aa** was obtained in 92% overall yield. Some of the results are summarized in Table 2.

Using the optimized reaction conditions, the reaction of **1** with various substituted anilines was studied and the results were listed in Table 3. As shown in the table, the length of fluoroalkyl chains had little influence on the reaction, but the reaction results were obviously affected by the

Table 3. Synthesis of 2-fluoroalkylquinolines from **1**

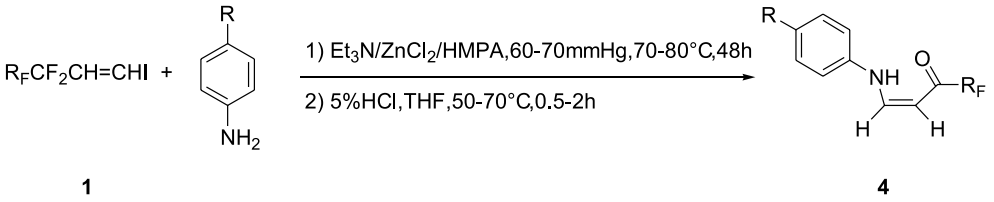


1 **3**

Entry	**1**	R	R_f	**3**	Yield (%)[a]
1	**1a**	MeO	C_3F_7	**3aa**	92
2	**1a**	Me	C_3F_7	**3ab**	87
3	**1b**	Me	C_3F_6Cl	**3bb**	83
4	**1c**	Me	CF_2Cl	**3cb**	85
5	**1d**	Me	C_5F_{11}	**3db**	75
6	**1a**	H	C_3F_7	**3ac**	79
7	**1a**	Cl	C_3F_7	**3ad**	75
8	**1a**	Br	C_3F_7	**3ae**	71
9	**1b**	Br	C_3F_6Cl	**3be**	75
10	**1a**	NO_2	C_3F_7	**3af**[b]	31

[a] Isolated yields based on **1**.
[b] Obtained directly from the first step without further treatment with acid.

Table 4. Synthesis of fluoroalkylated enaminoketones from **1**



1 **4**

Entry	**1**	R	R_f	**4**	Yields (%)[a]
1	**1a**	MeO	C_3F_7	**4aa**[b]	68
2	**1a**	Me	C_3F_7	**4ab**	74
3	**1b**	Me	C_3F_6Cl	**4bb**	73
4	**1c**	Me	CF_2Cl	**4cb**	64
5	**1d**	Me	C_5F_{11}	**4db**	73
6	**1b**	MeO	C_3F_6Cl	**4ba**[b]	68
7	**1b**	H	C_3F_6Cl	**4bc**	75
8	**1a**	H	C_3F_7	**4ac**	74
9	**1c**	H	CF_2Cl	**4cc**	71
10	**1b**	Cl	C_3F_6Cl	**4bd**	68
11	**1b**	Br	C_3F_6Cl	**4be**	68

[a] Isolated yields based on **1**.
[b] Hydrolysis was performed at 50 °C for 1 h.

substituent in anilines and better results were obtained with electron-donating substituents such as methoxy and methyl. In the case of *p*-nitroaniline, the reaction was kind of slow, and the yield of **3af** was very low due to its weak nucleophilicity caused by strong electron-withdrawing nitro group (entry 10).

Similarly, reaction of **1** with various anilines in HMPA in the presence of Et_3N and $ZnCl_2$ at 70–80 °C under a vacuum of 60–70 mmHg followed by the treatment of the product with 5% hydrochloric acid at 50–70 °C gave compound **4** in good overall yields. The results were summarized in Table 4. In the case of *p*-methoxyaniline, acidic hydrolysis was performed at 50 °C because cyclization products were formed at higher temperature. The reaction of **1a** with *p*-nitroaniline gave only cyclization product **3af**, and the corresponding fluoroalkylated enaminoaldehyde **2af** was not obtained. All fluoroalkylated enaminoketones obtained were in *Z*-configuration as indicated by the coupling constants ($J=7.3$–7.8 Hz) of the two olefinic protons in their ^{1}H NMR spectra. This is probably due to the formation of an intramolecular hydrogen bond between N–H and carbonyl oxygen. Similar result was reported in the literature.[19]

In conclusion, the reaction of 2-fluoroalkyl-1-iodoethylenes with various anilines and the subsequent acid promoted transformation of products are achieved under mild conditions, providing a convenient method for the preparation of 2-fluoroalkylquinolines and fluoroalkylated (*Z*-) enaminoketones. Compared to the reported procedures, this method has the advantage of easily available starting material, mild reaction conditions and good selectivity.

3. Experimental

3.1. General

Melting points were uncorrected. IR spectra were taken on a Perkin–Elmer jeol 983 spectrophotometer. ^{1}H NMR spectra were measured on a Bruker AM300 (300 MHz) spectrometer using TMS as internal standard. ^{19}F NMR spectra were taken on a Bruker AM300 (282 MHz) spectrometer. Chemical shifts were reported using $CFCl_3$ as external standard [$\delta(CFCl_3)=0$], upfield shift being designated as negative. Mass spectra were obtained on a Hewlett-Packard HP-5989A spectrometer. Column chromatography was performed using silica H, particle size 10–40 μ.

3.2. General procedure for the preparation of intermediate 2

A mixture of **1** (1 mmol), arylamine (3 mmol), Et_3N (5 mmol) and anhydrous $ZnCl_2$ (1 mmol) were stirred in HMPA (10 mL) at 70–80 °C under a vacuum of 60–70 mmHg. After 24–48 h, the mixture was cooled to room temperature, diluted with 1% HCl (15 mL) and then extracted with ether (3×20 mL). The organic layer was combined, washed with saturated NaCl solution and dried over sodium sulfate. After the solvent was removed by rotary evaporation, the residue was chromatographed on silica gel eluting with petroleum–ethyl ether to give **2**.

3.2.1. Data for compound 2aa. Yellow solid. Mp 108–110 °C. IR (KBr): 3231, 3120, 3036, 2903, 2841, 1623, 1587, 1519, 1412, 1350, 1289, 1220, 1181, 1146, 1079, 959, 830, 730 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 10.92 (br, 1H, NH), 9.69 (d, 1H, $J=8.4$ Hz), 9.39 (d, 1H, $J=2.7$ Hz), 7.13–7.08 (m, 4H), 6.95–6.85 (m, 4H), 6.22 (br, 1H, NH), 5.62 (d, 1H, $J=8.4$ Hz), 5.56 (d, 1H, $J=2.7$ Hz), 3.82 (s, 6H). ^{19}F NMR ($CDCl_3$): δ −80.28 (3F), −80.54 (3F), −110.71 (2F), −111.64 (2F), −125.19 (2F), −126.72 (2F). EIMS *m/z* (%): 345 (M^+, 57.08), 176 ($M^+-C_3F_7$, 100.00). EI-HRMS: calcd for $C_{13}H_{10}F_7NO_2$ [M^+] 345.0600, found 345.0612.

3.2.2. Data for intermediate C. IR (film): 3208, 3095, 3003, 2960, 2839, 1641, 1596, 1575, 1516, 1467, 1443, 1296, 1243, 1181, 1151, 1037, 824 cm^{-1}. ^{1}H NMR

(acetone-*d6*): δ 8.71 (br, 1H), 7.58 (br, d, *J*=13.5 Hz, 1H), 7.02–6.76 (m, 8H), 5.55 (d, *J*=13.5 Hz, 1H), 3.83 (s, 3H), 3.76 (s, 3H). ^{19}F NMR (acetone-*d6*): δ −80.54 (3F), −111.59 (2F), −125.78 (2F). EIMS *m/z* (%): 451 (M^++1, 52.01), 450 (M^+, 59.99), 328 (M^+−NHC_6H_4-OMe, 3.19), 281 (M^+−C_3F_7, 100.00). EI-HRMS: calcd for $C_{20}H_{17}F_7N_2O_2$ [M^+] 450.1170, found: 450.1158.

3.3. General procedure for the preparation of 2-fluoroalkylquinolines (3)

A mixture of **1** (1 mmol), arylamine (3 mmol), Et_3N (5 mmol) and anhydrous $ZnCl_2$ (1 mmol) were stirred in HMPA (10 mL) at 110 °C under a vacuum of 60–70 mmHg. After 24 h, the mixture was cooled to room temperature, diluted with 1% HCl (15 mL) and then extracted with ether (3×20 mL). The organic layer was combined, washed with saturated NaCl solution and dried over sodium sulfate. After the solvent was removed by rotary evaporation, the residue was dissolved in toluene (5 mL), and TsOH (0.1 mmol) was added. The mixture was stirred under reflux for 3–4 h (monitored by TLC). After the reaction was complete, the solvent was removed under vacuum, the residue was chromatographed on silica gel eluting with petroleum–ethyl ether to give **3** as a solid.

3.3.1. 2-Heptafluoropropyl-6-methoxyquinoline (3aa). Mp 70–72 °C. IR (KBr): 3018, 2965, 2938, 1627, 1593, 1506, 1485, 1386, 1230, 1109, 1032, 885, 854, 748 cm^{-1}. ^{1}H NMR (acetone-d6): δ 8.42 (d, 1H, *J*=9.0 Hz), 7.95 (d, 1H, *J*=9.0 Hz), 7.72 (d, 1H, *J*=9.0 Hz), 7.44–7.36 (m, 2H), 3.87 (s, 3H). ^{19}F NMR (acetone-d6): δ −81.37 (3F), −114.42 (2F), −127.18 (2F). EIMS *m/z* (%): 327 (M^+, 76.59), 308 (M^+−F, 10.92), 208 (M^+−C_2F_5, 100.00). EI-HRMS: calcd for $C_{13}H_8F_7NO$ [M^+] 327.0494, found 327.0479.

3.3.2. 6-Methyl-2-heptafluoropropylquinoline (3ab).[20] Mp 75–77 °C. IR (KBr): 3077, 2928, 1594, 1574, 1503, 1357, 1225, 1111, 931, 879, 836 cm^{-1}. ^{1}H NMR (acetone-d6): δ 8.72 (d, 1H, *J*=8.7 Hz), 8.23 (d, 1H, *J*=8.7 Hz), 8.03 (d, 2H, *J*=9.0 Hz), 7.94 (d, 1H, *J*=8.7 Hz), 2.74 (s, 3H). ^{19}F NMR (acetone-d6): δ −81.02 (3F), −114.33 (2F), −126.80 (2F).

3.3.3. 6-Methyl-2-(1,1,2,2,3,3-hexafluoro-3-chloropropyl)quinoline (3bb). Mp 50–52 °C. IR (KBr): 3030, 2971, 1595, 1499, 1320, 1193, 1112, 823, 760 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.25 (d, 1H, *J*=9.0 Hz), 8.15 (d, 1H, *J*=9.0 Hz), 7.71–7.65 (m, 3H), 2.60 (s, 3H). ^{19}F NMR ($CDCl_3$): δ −66.80 (2F), −112.81 (2F), −120.22 (2F). EIMS *m/z* (%): 329 (M^++2, 9.73), 327 (M^+, 28.85), 292 (M^+−Cl, 10.35), 192 (M^+−C_2F_4Cl, 100.00). EI-HRMS: calcd for $C_{13}H_8ClF_6N$ [M^+] 327.0250, found 327.0228.

3.3.4. 6-Methyl-2-chlorodifluoromethylquinoline (3cb). Mp 68–70 °C. IR (KBr): 3053, 2959, 1594, 1501, 1314, 1294, 1145, 1127, 1081, 965, 937, 833, 775, 734 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.26 (d, 1H, *J*=9.0 Hz), 8.13 (d, 1H, *J*=9.0 Hz), 7.74–7.66 (m, 3H), 2.60 (s, 3H). ^{19}F NMR ($CDCl_3$): δ −55.12 (s). EIMS *m/z* (%): 229 (M^++2, 9.43), 227 (M^+, 28.38), 192 (M^+−Cl, 100.00). EI-HRMS: calcd for $C_{11}H_8ClF_2N$ [M^+] 227.0313, found 227.0295.

3.3.5. 6-Methyl-2-undecafluoropentylquinoline (3db). Mp 64–66 °C. IR (KBr): 3064, 2978, 2918, 1599, 1502, 1364, 1243, 1205, 1137, 727, 663, 630 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.26 (d, 1H, *J*=9.0 Hz), 8.15 (d, 1H, *J*=9.0 Hz), 7.71–7.66 (m, 3H), 2.60 (s, 3H). ^{19}F NMR ($CDCl_3$): δ −81.20 (3F), −113.82 (2F), −122.11 (2F), −122.62 (2F), −126.51 (2F). EIMS *m/z* (%): 411 (M^+, 46.68), 392 (M^+−F, 10.69), 192 (M^+−C_4F_9, 100.00). EI-HRMS: calcd for $C_{15}H_8F_{11}N$ [M^+] 411.0481, found 411.0495.

3.3.6. 2-Heptafluoropropylquinoline (3ac).[21] Light yellow oil. IR (film): 3070, 1622, 1598, 1508, 1352, 1230, 1183, 1118, 1056, 911, 820, 757, 741 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.38 (d, 1H, *J*=8.7 Hz), 8.27 (d, 1H, *J*=8.7 Hz), 7.94–7.67 (m, 4H). ^{19}F NMR ($CDCl_3$): δ −80.40 (3F), −114.81 (2F), −126.42 (2F).

3.3.7. 2-Heptafluoropropyl-6-chloro-quinoline (3ad). Mp 112–115 °C. IR (KBr): 3045, 3071, 1597, 1498, 1466, 1355, 1286, 1230, 1116, 865, 831, 747 cm^{-1}. ^{1}H NMR (acetone-d6): δ 8.57 (d, 1H, *J*=9.0 Hz), 8.09 (d, 2H, *J*=9.0 Hz), 7.88–7.78 (m, 2H). ^{19}F NMR (acetone-d6): δ −81.01 (3F), −114.53 (2F), −126.82 (2F). EIMS *m/z* (%): 333 (M^++2, 15.66), 331 (M^+, 47.38), 312 (M^+−F, 7.42), 212 (M^+−C_2F_5, 100.00). EI-HRMS: calcd for $C_{12}H_5ClF_6N$ [$(M-F)^+$] 312.0015, found 312.0015.

3.3.8. 2-Heptafluoropropyl-6-bromoquinoline (3ae). Mp 126–128 °C. IR (KBr): 3042, 1595, 1496, 1465, 1355, 1286, 1230, 1116, 857, 829, 746 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.27 (d, 1H, *J*=8.7 Hz), 8.14–8.09 (m, 2H), 7.92–7.88 (m, 1H), 7.76 (d, 1H, *J*=8.7 Hz). ^{19}F NMR ($CDCl_3$): δ −80.39 (3F), −114.83 (2F), −126.36 (2F). EIMS *m/z* (%): 377 (M^++2, 46.18), 375 (M^+, 47.31), 356 (M^+−F, 5.89), 258 (97.11), 256 (M^+−C_2F_5, 100.00). EI-HRMS: calcd for $C_{12}H_5BrF_7N$ [M^+] 374.9494, found 374.9523.

3.3.9. 2-(1,1,2,2,3,3-Hexafluoro-3-chloropropyl)-6-bromoquinoline (3be). Mp 118–120 °C. IR (KBr): 3042, 1595, 1492, 1464, 1315, 1296, 1187, 1113, 797, 757 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 8.24 (d, 1H, *J*=9.0 Hz), 8.11–8.06 (m, 2H), 7.89–7.85 (m, 1H), 7.73 (d, 1H, *J*=9.0 Hz). ^{19}F NMR ($CDCl_3$): δ −67.20 (2F), −113.20 (2F), −120.43 (2F). EIMS *m/z* (%): 393 (M^++2, 46.15), 391 (M^+, 35.71), 372 (M^+−F, 2.18), 356 (M^+−Cl, 9.55), 258 (96.56), 256 (M^+−C_2F_4Cl, 100.00). EI-HRMS: calcd for $C_{12}H_5BrClF_6N$ [M^+] 390.9198, found 390.9174.

3.3.10. 2-Heptafluoropropyl-6-nitroquinoline (3af). Mp 140–143 °C. IR (KBr): 3099, 1628, 1608, 1549, 1502, 1355, 1284, 1230, 1117, 937, 817, 749 cm^{-1}. ^{1}H NMR (acetone-d6): δ 9.19 (d, 1H, *J*=2.4 Hz), 9.10 (d, 1H, *J*=9.0 Hz), 8.68 (dd, 1H, *J*=9.0, 2.4 Hz), 8.45 (d, 1H, *J*=9.0 Hz), 8.18 (d, 1H, *J*=9.0 Hz). ^{19}F NMR (acetone-d6): δ −81.30 (3F), −115.22 (2F), −127.01 (2F). EIMS *m/z* (%): 342 (M^+, 98.70), 296 (M^+−NO_2, 40.17), 223 (M^+−C_2F_5, 100.00), 177 (M^+−C_2F_5-NO_2, 48.78). EI-HRMS: calcd for $C_{12}H_5F_7N_2O_2$ [M^+] 342.0239, found 342.0207.

3.4. General procedure for the preparation of fluoroalkylated enaminoketones (4)

A mixture of **1** (1 mmol), arylamine (3 mmol), Et_3N

(5 mmol) and anhydrous $ZnCl_2$ (1 mmol) were stirred in HMPA (10 mL) at 80 °C under a vacuum of 60–70 mmHg. After 48 h, the mixture was cooled to room temperature, diluted with 1%HCl (15 mL) and then extracted with ether (3×20 mL). The organic layer was combined, washed with water and saturated NaCl solution and dried over sodium sulfate. After the solvent was removed by rotary evaporation, the residue was dissolved in THF (5 mL) and 5% HCl (1 mL) was added. The mixture was stirred at 50–70 °C for 0.5–2 h (monitored by ^{19}F NMR). After the reaction was complete, the mixture was cooled to room temperature, diluted with water (10 mL) and then extracted with ether (3×20 mL). The organic layer was combined, washed with water and saturated NaCl solution, and dried over sodium sulfate. After the solvent was removed, the residue was chromatographed on silica gel eluting with petroleum–ethyl ether to give **4** as a light yellow solid.

3.4.1. *cis*-4,4,5,5,6,6,6-Heptafluoro-1-(4-methoxyphenylamino)hex-1-en-3-one (4aa). Mp 58–60 °C. IR (KBr): 3015, 2966, 1643, 1598, 1565, 1494, 1301, 1243, 1212, 1120, 889, 835, 780, 752, 715 cm^{-1}. ^1H NMR ($CDCl_3$): δ 12.05 (br, 1H, NH), 7.58 (dd, 1H, J=13.2, 7.5 Hz), 7.10 (d, 2H, J=9.0 Hz), 6.93 (d, 2H, J=9.0 Hz), 5.68 (d, 1H, J=7.5 Hz), 3.83 (s, 3H). ^{19}F NMR ($CDCl_3$): δ −80.84 (3F), −121.43 (2F), −127.21 (2F). EIMS m/z (%): 345 (M^+, 46.42), 326 (M^+-F, 2.36), 176 ($M^+-C_3F_7$, 100.00). EI-HRMS: calcd for $C_{13}H_{10}F_7NO_2$ [M^+] 345.0600, found 345.0579.

3.4.2. *cis*-6-Chloro-4,4,5,5,6,6-hexafluoro-1-(4-methoxyphenylamino)hex-1-en-3-one (4ba).[19] Mp 70–72 °C. IR (KBr): 2966, 2843, 1645, 1598, 1565, 1493, 1289, 1182, 1122, 1035, 836, 770, 705 cm^{-1}. ^1H NMR ($CDCl_3$): δ 12.03 (br, 1H, NH), 7.57 (dd, 1H, J=13.2, 7.2 Hz), 7.10 (d, 2H, J=9.0 Hz), 6.93 (d, 2H, J=9.0 Hz), 5.68 (d, 1H, J=7.2 Hz), 3.83 (s, 3H). ^{19}F NMR ($CDCl_3$): δ −67.62 (2F), −119.84 (2F), −121.20 (2F).

3.4.3. *cis*-4,4,5,5,6,6,6-Heptafluoro-1-(tolylamino)hex-1-en-3-one (4ab).[20] Mp 63–64 °C. IR (KBr): 1644, 1598, 1565, 1496, 1305, 1233, 1212, 1120, 888, 815, 752 cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.96 (br, 1H, NH), 7.63 (dd, 1H, J=13.2, 7.5 Hz), 7.19 (d, 2H, J=8.4 Hz), 7.04 (d, 2H, J=8.4 Hz), 5.69 (d, 1H, J=7.5 Hz), 2.35 (s, 3H). ^{19}F NMR ($CDCl_3$): δ −81.02 (3F), −121.63 (2F), −127.41 (2F).

3.4.4. *cis*-6-Chloro-4,4,5,5,6,6-hexafluoro-1-(tolylamino)-hex-1-en-3-one (4bb). Mp 77–79 °C. IR (KBr): 2926, 1641, 1600, 1561, 1496, 1365, 1313, 1286, 1197, 1175, 1123, 812, 706 cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.98 (br, 1H, NH), 7.64 (dd, 1H, J=13.2, 7.2 Hz), 7.21 (d, 2H, J=8.4 Hz), 7.05 (d, 2H, J=8.4 Hz), 5.69 (d, 1H, J=7.2 Hz), 2.36 (s, 3H). ^{19}F NMR ($CDCl_3$): δ −67.67 (2F), −119.93 (2F), −121.26 (2F). EIMS m/z (%): 347 (M^++2, 13.92), 345 (M^+, 42.31), 310 (M^+-Cl, 7.27), 160 ($M^+-C_3F_6Cl$, 100.00). EI-HRMS: calcd for $C_{13}H_{10}ClF_6NO$ [M^+] 345.0355, found 345.0357.

3.4.5. *cis*-1-Chloro-1,1-difluoro-4-(tolylamino)but-3-en-2-one (4cb).[22] Mp 72–74 °C. IR (KBr): 2805, 1641, 1602, 1568, 1494, 1310, 1211, 1157, 1141, 1074, 945, 900, 757, 713 cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.76 (br, 1H, NH), 7.65 (dd, 1H, J=13.2, 7.5 Hz), 7.21 (d, 2H, J=8.4 Hz), 7.04 (d, 2H, J=8.4 Hz), 5.64 (d, 1H, J=7.5 Hz), 2.36 (s, 3H). ^{19}F NMR ($CDCl_3$): δ −65.20 (s).

3.4.6. *cis*-4,4,5,5,6,6,7,7,8,8,8-Undecafluoro-1-(tolylamino)oct-1-en-3-one (4db). Mp 94–95 °C. IR (KBr): 1647, 1598, 1563, 1496, 1310, 1197, 1143, 811, 778, 746 cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.98 (br, 1H, NH), 7.65 (dd, 1H, J=13.2, 7.5 Hz), 7.21 (d, 2H, J=8.4 Hz), 7.05 (d, 2H, J=8.4 Hz), 5.70 (d, 1H, J=7.5 Hz), 2.36 (s, 3H). ^{19}F NMR ($CDCl_3$): δ −81.01 (3F), −120.52 (2F), −122.84 (4 F), −126.50 (2F). EIMS m/z (%): 429 (M^+, 38.30), 410 (M^+-F, 3.47), 160 ($M^+-C_5F_{11}$, 100.00). Anal. calcd for $C_{15}H_{10}F_{11}NO$: C, 41.97; H, 2.35; N, 3.26. Found C, 42.30; H, 2.60; N, 3.24.

3.4.7. *cis*-6-Chloro-4,4,5,5,6,6-hexafluoro-1-(phenylamino)hex-1-en-3-one (4bc). Mp 73–75 °C. IR (KBr): 3076, 1647, 1610, 1581, 1486, 1290, 1194, 1113, 754, 710 cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.94 (br, 1H, NH), 7.68 (dd, 1H, J=13.2, 7.5 Hz), 7.44–7.39 (m, 2H), 7.25–7.14 (m, 3H), 5.73 (d, 1H, J=7.5 Hz). ^{19}F NMR ($CDCl_3$): δ −67.63 (2F), −119.94 (2F), −121.21 (2F). EIMS m/z (%): 333 (M^++2, 9.44), 331 (M^+, 27.77), 146 ($M^+-C_3F_6Cl$, 100.00). MALDI-HRMS: calcd for $C_{12}H_9ClF_6NO$ [(M+H)$^+$] 332.0271, found 332.0282.

3.4.8. *cis*-4,4,5,5,6,6,6-Heptafluoro-1-(phenylamino)hex-1-en-3-one (4ac).[10] Mp 48–50 °C. IR (KBr): 3120, 3050, 1648, 1605, 1581, 1489, 1459, 1309, 1216, 1122, 888, 777, 753, 720 cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.96 (br, 1H, NH), 7.68 (dd, 1H, J=13.2, 7.5 Hz), 7.44–7.38 (m, 2H), 7.27–7.15 (m, 3H), 5.73 (d, 1H, J=7.5 Hz). ^{19}F NMR ($CDCl_3$): δ −80.82 (3F), −121.54 (2F), −127.21 (2F).

3.4.9. *cis*-1-Chloro-1,1-difluoro-4-(phenylamino)but-3-en-2-one (4cc). Mp 88–90 °C. IR (KBr): 3249, 1675, 1604, 1565, 1483, 1370, 1303, 1209, 1139, 1071, 954, 754 cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.73 (br, 1H, NH), 7.69 (dd, 1H, J=13.2, 7.5 Hz), 7.43–7.37 (m, 2H), 7.23–7.12 (m, 3H), 5.67 (d, 1H, J=7.5 Hz). ^{19}F NMR ($CDCl_3$): δ −65.30 (s). EIMS m/z (%): 233 (M^++2, 6.40), 231 (M^+, 19.53), 146 (M^+-CF_2Cl, 100.00). Anal. calcd for $C_{10}H_8ClF_2NO$: C, 51.85; H, 3.48; N, 6.05. Found C, 52.06; H, 3.77; N, 5.89.

3.4.10. *cis*-6-Chloro-4,4,5,5,6,6-hexafluoro-1-(4-chlorophenylamino)hex-1-en-3-one (4bd). Mp 62–64 °C. IR (KBr): 1639, 1593, 1558, 1488, 1306, 1287, 1177, 829, 771 cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.90 (br, 1H, NH), 7.60 (dd, 1H, J=13.2, 7.5 Hz), 7.39 (d, 2H, J=9.0 Hz), 7.10 (d, 2H, J=9.0 Hz), 5.75 (d, 1H, J=7.5 Hz). ^{19}F NMR ($CDCl_3$): δ −67.44 (2F), −119.72 (2F), −120.92 (2F). EIMS m/z (%): 367 (M^++2, 29.25), 365 (M^+, 45.10), 180 ($M^+-C_3F_6Cl$, 100.00). EI-HRMS: calcd for $C_{12}H_7Cl_2F_6NO$ [M^+] 364.9809, found 364.9797.

3.4.11. *cis*-6-Chloro-4,4,5,5,6,6-hexafluoro-1-(4-bromophenylamino)hex-1-en-3-one (4be). Mp 80–82 °C. IR (KBr): 1639, 1593, 1558, 1585, 1305, 1286, 1178, 827, 771 cm^{-1}. ^1H NMR ($CDCl_3$): δ 11.86 (br, 1H, NH), 7.61 (dd, 1H, J=13.2, 7.8 Hz), 7.52 (d, 2H, J=9.0 Hz), 7.03 (d, 2H, J=9.0 Hz), 5.75 (d, 1H, J=7.8 Hz). ^{19}F NMR ($CDCl_3$) δ −67.73 (2F), −120.02 (2F), −121.23 (2F). EIMS m/z

(%): 411 ($M^+ + 2$, 57.78), 409 (M^+, 44.42), 224 ($M^+ - C_3F_6Cl$, 86.08), 145 ($M^+ - C_3F_6Cl$–Br, 100.00). EI-HRMS: calcd for $C_{12}H_7BrClF_6NO$ [M^+] 408.9304, found 408.9330.

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