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A straightforward preparation of fluorine-containing 1,2-dihydropyrimidines and pyrimidines with 2,2-dihydropolyfluoroalkylaldehydes

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Abstract—The reactions of 2,2-dihydropolyfluoroalkylaldehydes with ammonia and enol ethers or carbonyl compounds are described. In the presence of zinc chloride, all reactions took place readily in THF at 50 °C to give fluorine-containing 1,2-dihydropyrimidines in moderate to good yields. Dehydrogenation of the resulting fluorine-containing 1,2-dihydropyrimidines with tetrachloro-1,4-benzoquinone (TCBQ) or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) at room temperature afforded the corresponding fluorine-containing pyrimidines in good yields.

1. Introduction

The ability of fluorine atom to enhance biological and therapeutic activities of certain organic compounds has led to a widespread interest in selective introduction of fluorine atom and fluoroalkyl groups into organic molecules, especially those heterocyclic compounds which have potential biological activities.[1] It is known that 1,2-dihydropyrimidine and pyrimidine are important heterocyclic moieties in both natural and synthetic compounds with biological properties.[2] Accordingly many methods have been developed for their synthesis.[3] However, fluorine-containing 1,2-dihydropyrimidines, which may have potential biological activities are less studied.[4] In this paper we report a convenient synthesis of fluorine-containing 1,2-dihydropyrimidines and pyrimidines from 2,2-dihydropolyfluoroalkylaldehydes.[5]

2. Results and discussion

Recently, it was found in our laboratory that both the reaction of 2,2-dihydropolyfluoroalkylaldehydes with amines and the reaction of perfluoroalkyl iodides with amines and ethyl vinyl ether in the presence of sodium dithionite gave the corresponding perfluoroalkylated enaminoketones.[6] However, when ammonia was used instead of amine to react with perfluorobutyl iodide (**1a**) and ethyl vinyl ether, a new compound was obtained along with the desired product (Scheme 1). Spectral analyses and X-ray crystallography showed that it was 2-methyl-4-heptafluoropropyl-1,2-dihydropyrimidine **2a** (Fig. 1).[7]

From the structure of **2a**, it was supposed that this by-product was formed by the reaction of **1a** with 2 equiv of ethyl vinyl ether and 2 equiv of ammonia. To confirm this hypothesis, different amounts of ethyl vinyl ether were tested in the presence of excess ammonia. As shown in Table 1, the yield of **2a** increased gradually with the addition of more ethyl vinyl ether, but it did not change obviously when more than 2 equiv of ethyl vinyl ether was used. Similar results were obtained with other perfluoroalkyl iodides (Table 1). In all reactions, the yields of **2** were relatively low.

It is known that the reaction of perfluoroalkyl iodides and ethyl vinyl ether initiated by sodium dithionite affords 2,2-dihydropolyfluoroalkylaldehydes (**3**). Referring to the above results, we proposed that compound **3** was involved in the reaction as an intermediate. In the presence of sodium dithionite, **1** reacted with ethyl vinyl ether first to give **3**, which reacted with another ethyl vinyl ether and ammonia

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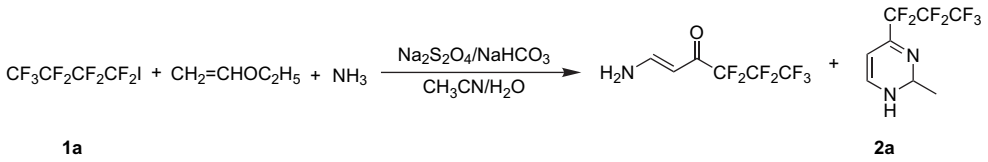


Scheme 1.

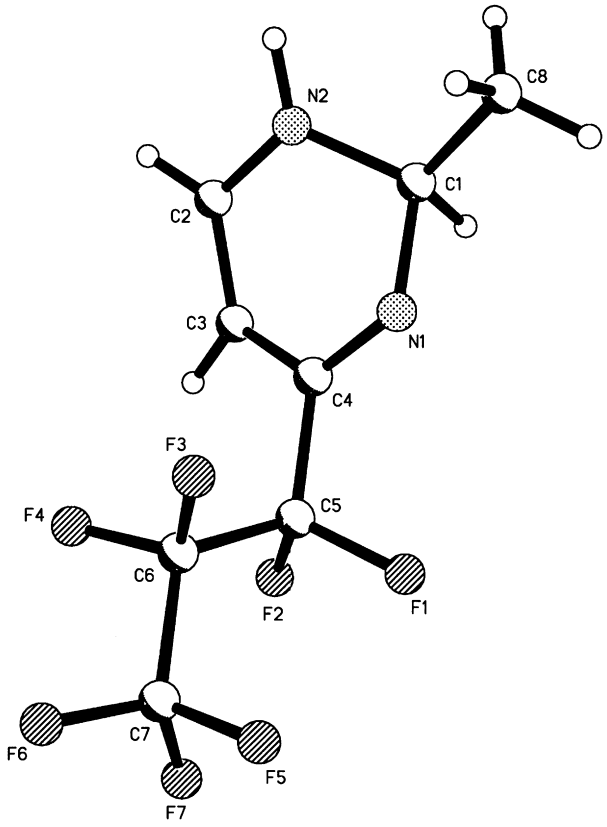
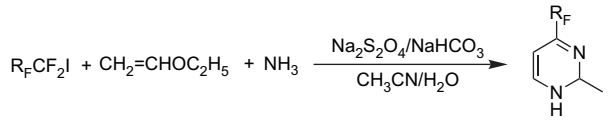


Figure 1. Crystal structure of **2a**.

to afford the final product **2** (Scheme 2). Compound **3** is an important intermediate in organic synthesis and has been used for the preparation of many fluorine-containing compounds.[6a,8] To make the reaction simple and improve the yield of **2**, the reaction of **3** with ammonia and ethyl vinyl ether was then studied. It was found that **2** was obtained as expected and the yield could be improved significantly by the addition of anhydrous zinc chloride. Gaseous ammonia gave higher yields than aqueous ammonia. The results are summarized in Table 2.

Under similar conditions, trimethylsilyl enol ethers **4** could also react with **3** and ammonia to give the corresponding 4-perfluoroalkyl-1,2-dihydropyrimidines in moderate to good yields (Scheme 3). The results are listed in Table 3. It was interesting that spiral products **2h** and **2i** were obtained from 1-cyclohexenyl trimethylsilyl ether **4e** in reasonable yields, while the reaction of 1-cyclopentyl trimethylsilyl ether **4f** with **3** and ammonia was very complicated

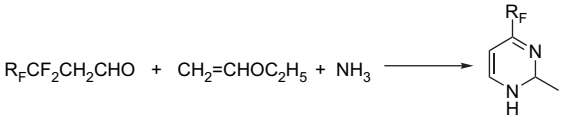
Table 1. The reaction of **1** with ethyl vinyl ether and ammonia[a]



Entry	**1** (R_F)	Ethyl vinyl ether/**1** (mol)	Product	Yield[b] (%)
1	**1a** (C_3F_7)	1.2:1	**2a**	8
2	**1a** (C_3F_7)	1.5:1	**2a**	18
3	**1a** (C_3F_7)	2.0:1	**2a**	25
4	**1a** (C_3F_7)	2.5:1	**2a**	25
5	**1b** (ClC_3F_6)	1.2:1	**2b**	7
6	**1b** (ClC_3F_6)	2.0:1	**2b**	27
7	**1c** (CF_3)	1.5:1	**2c**	19
8	**1c** (CF_3)	2.0:1	**2c**	28

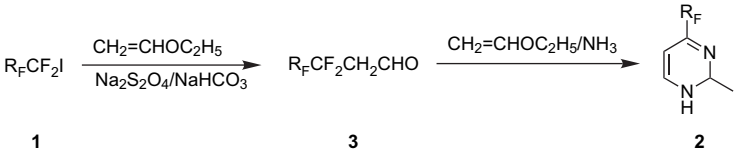
[a] Reaction conditions: **1** (1 mmol), sodium dithionite (9 mmol), sodium dicarbonate (8 mmol), aqueous ammonia solution (25%, 5 mL).
[b] Isolated yields based on **1**.

Table 2. The reaction of **3** with ammonia and ethyl vinyl ether[a]



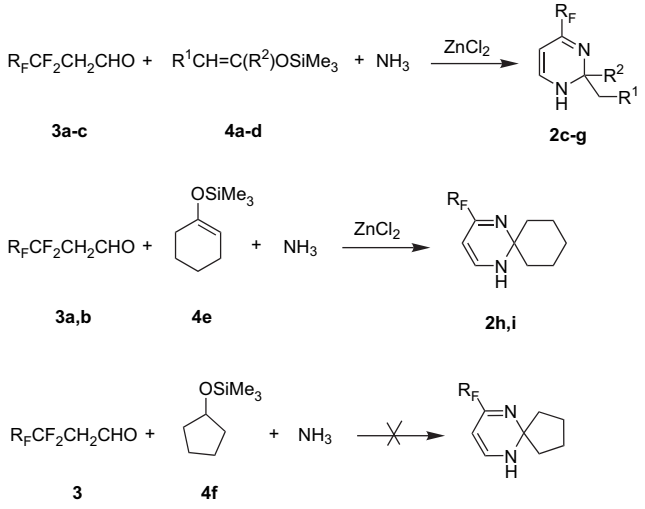
Entry	**3** (R_F)	Condition	Product	Yield[b] (%)
1	**3a** (C_3F_7)	NH_3 (aq)	**2a**	31
2	**3a** (C_3F_7)	NH_3 (g)	**2a**	34
3	**3a** (C_3F_7)	$ZnCl_2$, NH_3 (aq)	**2a**	51
4	**3a** (C_3F_7)	$ZnCl_2$, NH_3 (g)	**2a**	71
5	**3c** (CF_3)	$ZnCl_2$, NH_3 (g)	**2c**	61
6	**3b** (ClC_3F_6)	$ZnCl_2$, NH_3 (g)	**2b**	72

[a] Reaction conditions: **3** (1 mmol), ethyl vinyl ether (1.5 mmol), and excess ammonia in THF (20 mL) at 50 °C.
[b] Isolated yields based on **3**.



Scheme 2.

and no desired product was isolated, probably due to the strong angle tension of compound **4f**.



Scheme 3.

Table 3. The reaction of **3** with ammonia and trimethylsilyl enol ether[a]

Entry	3	$R^1CH{=}C(R^2)OSiMe_3$	Product	Yield[b] (%)
1	**3c**	**4a** (R^1=H, R^2=H)	**2c**	59
2	**3c**	**4b** (R^1=Et, R^2=H)	**2d**	54
3	**3a**	**4b** (R^1=Et, R^2=H)	**2e**	61
4	**3a**	**4c** (R^1=H, R^2=Me)	**2f**	70
5	**3b**	**4d** (R^1=Me, R^2=Me)	**2g**	45
6	**3a**	**4e**	**2h**	70
7	**3b**	**4e**	**2i**	71

[a] Reaction conditions: **3** (1 mmol), **4** (1.5 mmol), $ZnCl_2$ (1 mmol), and excess ammonia in THF (20 mL) at 50 °C.
[b] Isolated yields based on **3**.

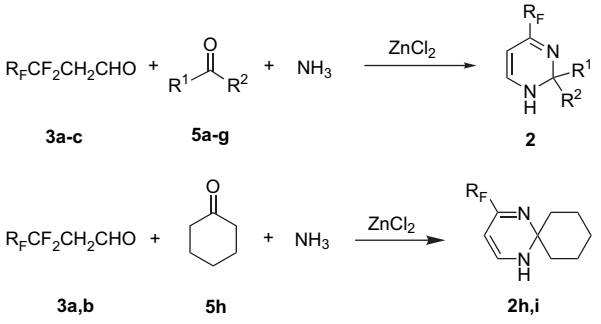
Considering the similarity of carbonyl compounds and their corresponding trimethylsilyl enol ethers in chemical properties, reactions of **3** with ammonia and aldehydes or ketones in the presence of zinc chloride were investigated next. As shown in Table 4, both aliphatic aldehydes and ketones reacted readily with **3** and ammonia to give the desired products in good yields, providing a more convenient method to synthesize these fluorine-containing 1,2-dihydropyrimidines. Again the reaction of cyclohexanone (**5h**) with **3** and ammonia gave the corresponding spiral products in good yields and no desired product was obtained in the case of cyclopentanone (Scheme 4). The reaction of aromatic aldehydes or ketones under similar conditions was

Table 4. The reaction of **3** with ammonia and carbonyl compounds[a]

Entry	3	Carbonyl compound	Product	Yield[b] (%)
1	**3c**	**5a** (CH_3CHO)	**2c**	63
2	**3a**	**5a** (CH_3CHO)	**2a**	74
3	**3c**	**5b** (C_3H_7CHO)	**2d**	61
4	**3a**	**5b** (C_3H_7CHO)	**2e**	64
5	**3b**	**5b** (C_3H_7CHO)	**2j**	63
6	**3a**	**5c** ($(CH_3)_2CHCHO$)	**2k**	65
7	**3a**	**5d** (CH_3COCH_3)	**2f**	75
8	**3a**	**5e** ($CH_3COC_2H_5$)	**2l**	63
9	**3a**	**5f** ($CH_3COC_3H_7$)	**2m**	62
10	**3a**	**5g** ($PhCOCH_3$)	**2n**	10
11	**3a**	**5h**	**2h**	77
12	**3b**	**5h**	**2i**	77

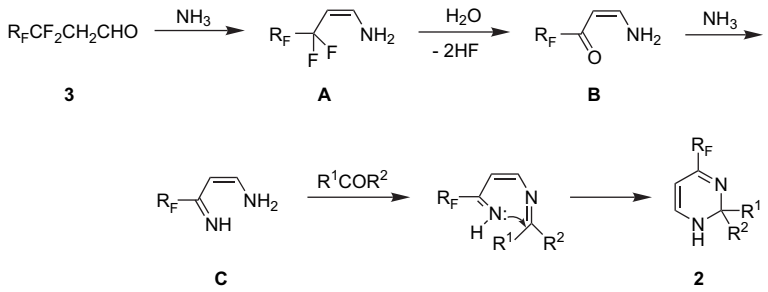
[a] Reaction conditions: **3** (1 mmol), **5** (1.5 mmol), $ZnCl_2$ (1 mmol), and excess ammonia in THF (20 mL) at 50 °C.
[b] Isolated yields based on **3**.

complicated and no desired product or very low yield was obtained (Table 4, entry 10).

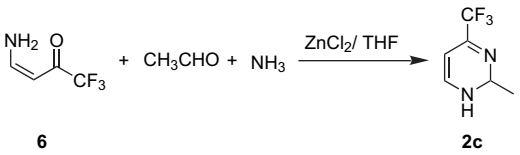


Scheme 4.

A possible mechanism was proposed for the reaction of **3** with **5** and ammonia as shown in Scheme 5. The reaction of **3** with ammonia gave intermediate **A**. Under basic conditions **A** underwent hydrolyzation to give intermediate **B**, which reacted further with ammonia to afford intermediate **C**. Subsequent condensation of **C** and **5** followed by the addition of NH to C=N double bond resulted in the formation of the final product. As a proof, the key intermediate, 4-amino-1,1,1-trifluoro-3-buten-2-one (**6**) was isolated from the reaction of **3c** and ammonia. Furthermore, **6** was allowed to react with **5a** and ammonia in the presence of $ZnCl_2$ under similar conditions and **2c** was obtained in moderate yield (Scheme 6). The precise role of $ZnCl_2$ in this reaction was not very clear. It was tentatively believed that it activated the reaction substrate by coordination with oxygen atom



Scheme 5.



6 2c

Scheme 6.

and the coordination of zinc ion with both oxygen of carbonyl group and ammonia facilitated the formation of intermediate **C**. Other Lewis acids such as $FeCl_3$, $AlCl_3$, and $BF_3 \cdot Et_2O$ were also tried in the reaction, only $BF_3 \cdot Et_2O$ gave comparable yield (Table 5).

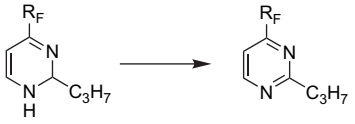
Table 5. The effect of Lewis acids on the reaction[a]

Entry	3	5	Lewis acid	Products	Yield[b] (%)
1	**3a**	**5b**	—	**2e**	31
2	**3a**	**5b**	$ZnCl_2$	**2e**	64
3	**3a**	**5b**	$AlCl_3$	**2e**	33
4	**3a**	**5b**	$FeCl_3$	**2e**	37
5	**3a**	**5b**	$BF_3 \cdot Et_2O$	**2e**	57

[a] Reaction conditions: **3** (1 mmol), **5** (1.5 mmol), Lewis acid (1 mmol), and excess ammonia in THF (20 mL) at 50 °C.
[b] Isolated yields based on **3**.

Compound **2** was very easy to be converted into the corresponding pyrimidine. Taking **2e** and **2j** as examples, treatment of **2e** and **2j** with tetrachloro-1,4-benzoquinone (TCBQ) or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) at room temperature for 24 h gave perfluoroalkylated pyrimidines **7** in good yields. The results are summarized in Table 6.

Table 6. Dehydrogenation of **2** with TCBQ or DDQ[a]



2e,j **7e,j**

Entry	2	Reagent	Condition	Product	Yield[b] (%)
1	**2e**	TCBQ	MeCN, rt, 24 h	**7e**	78
2	**2j**	TCBQ	MeCN, rt, 24 h	**7j**	83
3	**2e**	DDQ	CH_2Cl_2, rt, 24 h	**7e**	85
4	**2j**	DDQ	CH_2Cl_2, rt, 24 h	**7j**	82

[a] Reaction conditions: **2** (10 mmol), TCBQ or DDQ (15 mmol), and solvent (50 mL) at room temperature.
[b] Isolated yields based on **2**.

3. Conclusions

In summary, a convenient method has been developed for the synthesis of perfluoroalkylated 1,2-dihydropyrimidines and pyrimidines. In the presence of zinc chloride, a series of carbonyl compounds and enol ethers reacted readily with 2,2-dihydropolyfluoroalkylaldehydes and ammonia under mild conditions to give the corresponding perfluoroalkylated 1,2-dihydropyrimidines in moderate to good yields. Dehydrogenation of these fluorine-containing 1,2-dihydropyrimidines with tetrachloro-1,4-benzoquinone (TCBQ) or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) at room temperature afforded perfluoroalkylated pyrimidines.

4. Experimental section

4.1. General experimental methods

Melting points were uncorrected. IR spectra were taken on a Perkin–Elmer Jeol 983 spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker AM300 (300 MHz) spectrometer with TMS as internal standard. ^{19}F NMR spectra were recorded on a Bruker AM300 (282 MHz) spectrometer with $CFCl_3$ as external standard. Mass spectra were taken on an HP 5989A spectrometer. High-resolution mass data were obtained on a Finnigan MAT 8430 spectrometer. Column chromatography was performed using silica gel H, particle size 10–40 μm.

4.2. The reaction of 1 with ethyl vinyl ether and ammonia

To a mixture of **1** (10 mmol), ethyl vinyl ether (15 mmol), acetonitrile (25 mL), and water (25 mL), was added a mixture of sodium dithionite (9 mmol) and sodium dicarbonate (8 mmol) in portion under stirring at 0 °C. After addition the mixture was stirred at 0 °C for 10 min. Aqueous ammonia solution (25%, 5 mL) was added and the resulting mixture was stirred for 2 h at room temperature and 2 h at 50 °C. After the reaction was complete (monitored by ^{19}F NMR), the mixture was extracted with ethyl acetate (3×30 mL), the combined organic layer was washed with water and dried over anhydrous Na_2SO_4. The solvent was removed under reduced pressure and the crude product was purified by column chromatography (ethyl acetate and petroleum ether) to give compound **2**.

4.2.1. 2-Methyl-4-heptafluoropropyl-1,2-dihydropyrimidine (2a). White solid, mp: 79–81 °C. IR (KBr): 3153, 3018, 2946, 2857, 1613, 1545, 1495, 1354, 1287, 1221, 1186, 1118 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.92 (1H, d, J=6.6 Hz), 5.39 (1H, d, J=6.6 Hz), 4.92 (1H, q, J=6.3 Hz), 4.20 (1H, br s), 1.58 (3H, d, J=6.3 Hz). ^{19}F NMR ($CDCl_3$): δ −80.7 (3F, m), −117.7 (2F, m), −127.1 (2F, m). EIMS (*m*/*z*, %): 265 (M^++1, 2), 264 (M^+, 13), 249 (M^+-CH_3, 100), 69 (CF_3^+, 36). Anal. Calcd for $C_8H_7F_7N_2$: C, 36.37; H, 2.67; N, 10.60. Found: C, 36.51; H, 2.87; N, 10.38.

4.2.2. 2-Methyl-4-(3-chloro-1,1,2,2,3,3-hexafluoropropyl)-1,2-dihydropyrimidine (2b). Colorless oil. IR (film): 3148, 3016, 2942, 2844, 1612, 1544, 1495, 1133, 1120 cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 6.92 (1H, d, J=6.3 Hz), 5.39 (1H, d, J=6.3 Hz), 4.90 (1H, q, J=6.0 Hz), 3.62 (1H, br s), 1.57 (3H, d, J=6.3 Hz). ^{19}F NMR ($CDCl_3$): δ −67.3 (2F, m), −115.1 (2F, m), −121.1 (2F, m). EIMS (*m*/*z*, %): 280 (M^+, 12), 265 (M^+-Me, 100). Anal. Calcd for $C_8H_7ClF_6N_2$: C, 34.24; H, 2.51; N, 9.98. Found: C, 34.47; H, 2.54; N, 10.04.

4.2.3. 2-Methyl-4-trifluoromethyl-1,2-dihydropyrimidine (2c). White solid, mp: 59–61 °C. IR (KBr): 3149,

3020, 2983, 2955, 1615, 1546, 1501, 1448, 1388, 1350, 1313, 1222, 1193, 1133, 1094, 1069, 742 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.93 (1H, d, J=6.6 Hz), 5.37 (1H, d, J=6.6 Hz), 4.82 (1H, q, J=6.0 Hz), 3.62 (1H, br s), 1.57 (3H, d, J=6.0 Hz). ^{19}F NMR ($CDCl_3$): δ −71.8 (3F, m). EIMS (*m*/*z*, %): 164 (M^+, 22), 149 (M^+−Me, 100). Anal. Calcd for $C_6H_7F_3N_2$: C, 43.91; H, 4.30; F, 34.73; N, 17.07. Found: C, 43.95; H, 4.32; F, 34.78; N, 17.01.

4.3. The reaction of 3 with ammonia and ethyl vinyl ether

A mixture of **3** (1 mmol) and $ZnCl_2$ (1 mmol) in THF (10 mL) was stirred under ammonia atmosphere for 2 h at room temperature. Then a solution of ethyl vinyl ether (1.5 mmol) in THF (10 mL) was added dropwise. The resulting mixture was stirred at 50 °C under ammonia atmosphere for a few hours (monitored by ^{19}F NMR). After cooling, 20 mL water was added and the solution was extracted with ethyl acetate (3×10 mL). The combined organic layer was washed with water and dried over anhydrous Na_2SO_4. After removal of solvent, the crude product was purified by column chromatography (ethyl acetate and petroleum ether) to give **2**.

The procedure for the reaction of **3** with ammonia and **4** or **5** was similar to the above one.

4.3.1. 2-Propyl-4-trifluoromethyl-1,2-dihydropyrimidine (2d). Colorless oil. IR (film): 3207, 3039, 2964, 1629, 1542, 1467, 1325, 1191, 1142, 1095, 744 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.92 (1H, d, J=6.6 Hz), 5.34 (1H, d, J=6.6 Hz), 4.71 (1H, t, J=5.1 Hz), 4.55 (1H, br s), 1.86–1.81 (2H, m), 1.51–1.42 (2H, m), 0.96 (3H, t, J=6.2 Hz). ^{19}F NMR ($CDCl_3$): δ −71.7 (3F, m). EIMS (*m*/*z*, %): 192 (M^+, 5), 149 (M^+−Pr, 100), 123 (M^+−CF_3, 2). Anal. Calcd for $C_8H_{11}F_3N_2$: C, 50.00; H, 5.77; F, 29.66; N, 14.58. Found: C, 50.17; H, 5.88; F, 28.67; N, 14.18.

4.3.2. 2-Propyl-4-heptafluoropropyl-1,2-dihydropyrimidine (2e). White solid, mp: 44–46 °C. IR (KBr): 3218, 2966, 1626, 1572, 1537, 1462, 1302, 1181, 1128, 837 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.89 (1H, d, J=6.6 Hz), 5.34 (1H, d, J=6.6 Hz), 4.80 (1H, t, J=6.3 Hz), 4.50–4.00 (1H, br s), 1.91–1.80 (2H, m), 1.52–1.44 (2H, m), 0.98 (3H, t, J=6.3 Hz). ^{19}F NMR ($CDCl_3$): δ −80.7 (3F, m), −117.8 (2F, m), −127.1 (2F, m). EIMS (*m*/*z*, %): 292 (M^+, 2), 249 (M^+−C_3H_7, 100). Anal. Calcd for $C_{10}H_{11}F_7N_2$: C, 41.11; H, 3.79; N, 9.59. Found: C, 41.18; H, 3.84; N, 9.44.

4.3.3. 2,2-Dimethyl-4-heptafluoropropyl-1,2-dihydropyrimidine (2f). White solid, mp: 64–66 °C. IR (KBr): 3217, 1628, 1548, 1504, 1353, 1182, 1121, 900, 735 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.79 (1H, d, J=6.3 Hz), 5.22 (1H, d, J=6.3 Hz), 4.30–3.90 (1H, br s), 1.46 (6H, s). ^{19}F NMR ($CDCl_3$): δ −80.7 (3F, m), −118.6 (2F, m), −127.3 (2F, m). EIMS (*m*/*z*, %): 278 (M^+, 9), 263 (M^+−CH_3, 100), 144 (13). Anal. Calcd for $C_9H_9F_7N_2$: C, 38.68; H, 3.26; N, 10.07. Found: C, 38.74; H, 3.37; N, 9.91.

4.3.4. 2-Methyl-2-ethyl-4-(3-chloro-1,1,2,2,3,3-hexafluoropropyl)-1,2-dihydropyrimidine (2g). Colorless oil. IR (film): 3264, 2978, 1631, 1542, 1184, 1125, 840, 811 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.75 (1H, d, J=5.7 Hz), 5.13 (1H, d, J=5.7 Hz), 4.20 (1H, br s), 1.95–1.61(2H, m), 1.38 (3H, s), 0.92 (3H, t, J=6.3 Hz). ^{19}F NMR ($CDCl_3$): δ −67.4 (2F, m), −116.8 (2F, m), −121.2 (2F, m). EIMS (*m*/*z*, %): 308 (M^+, 2), 293 (M^+−Me, 13), 279 (M^+−Et, 100). Anal. Calcd for $C_{10}H_{11}ClF_6N_2$: C, 38.91; H, 3.59; N, 9.08. Found: C, 38.74; H, 3.42; N, 8.99.

4.3.5. 2-Heptafluoropropyl-1,5-diazaspiro[5.5]undeca-1,3-diene (2h). White solid, mp: 71–73 °C. IR (KBr): 3277, 2942, 1628, 1535, 1352, 1247, 1197, 1116, 892, 737 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.79 (1H, d, J=5.4 Hz), 5.21 (1H, d, J=5.4 Hz), 1.80–1.40 (10H, m). ^{19}F NMR ($CDCl_3$): δ −80.6 (3F, m), −118.1 (2F, m), −127.1 (2F, m). EIMS (*m*/*z*, %): 318 (M^+, 17), 275 (100). Anal. Calcd for $C_{12}H_{13}F_7N_2$: C, 45.29; H, 4.12; N, 8.80. Found: C, 45.28; H, 4.05; N, 8.64.

4.3.6. 2-(3-Chloro-1,1,2,2,3,3-hexafluoropropyl)-1,5-diazaspiro[5.5]undeca-1,3-diene (2i). White solid, mp: 70–72 °C. IR (KBr): 3223, 2940, 1625, 1537, 1496, 1305, 1198, 1125, 812 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.73 (1H, d, J=5.4 Hz), 5.21 (1H, d, J=5.4 Hz), 1.90–1.40 (10H, m). ^{19}F NMR ($CDCl_3$): δ −67.3 (2F, m), −116.8 (2F, m), −121.2 (2F, m). EIMS (*m*/*z*, %): 336 (M^++2, 7), 334 (M^+, 21), 275 (100). Anal. Calcd for $C_{12}H_{13}ClF_6N_2$: C, 43.06; H, 3.92; N, 8.37. Found: C, 42.93; H, 4.08; N, 7.99. ESI-HR calcd for $C_{12}H_{13}N_2ClF_6Na^+$: 357.0563. Found: 357.0564.

4.3.7. 2-Propyl-4-(3-chloro-1,1,2,2,3,3-hexafluoropropyl)-1,2-dihydropyrimidine (2j). White solid, mp: 45–47 °C. IR (KBr): 3217, 2966, 1626, 1572, 1539, 1467, 1309, 1184, 1126, 990, 837 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.89 (1H, d, J=6.6 Hz), 5.32 (1H, d, J=6.6 Hz), 4.79 (1H, t, J=6.3 Hz), 1.87–1.80 (2H, m), 1.50–1.43 (2H, m), 0.96 (3H, t, J=6.2 Hz). ^{19}F NMR ($CDCl_3$): δ −67.4 (2F, m), −116.2 (2F, m), −121.2 (2F, m). EIMS (*m*/*z*, %): 309 (M^++1, 15), 308 (M^+, 8), 265 (M^+−C_3H_7, 100). Anal. Calcd for $C_{10}H_{11}ClF_6N_2$: C, 38.91; H, 3.59; N, 9.08. Found: C, 39.20; H, 3.56; N, 8.91.

4.3.8. 2-*iso*-Propyl-4-heptafluoropropyl-1,2-dihydropyrimidine (2k). White solid, mp: 50–52 °C. IR (KBr): 3215, 2941, 1628, 1547, 1501, 1353, 1182, 1121 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.91 (1H, d, J=6.3 Hz), 5.31 (1H, d, J=6.3 Hz), 4.54 (1H, d, J=5.7 Hz), 2.24–2.18 (1H, m), 1.04–0.99 (6H, m). ^{19}F NMR ($CDCl_3$): δ −80.4 (3F, m), −116.7 (2F, m), −127.1 (2F, m). EIMS (*m*/*z*, %): 292 (M^+, 4), 275 (100), 249 (M^+−C_3H_7, 38). Anal. Calcd for $C_{10}H_{11}F_7N_2$: C, 41.11; H, 3.79; N, 9.59. Found: C, 40.98; H, 3.85; N, 9.19.

4.3.9. 2-Methyl-2-ethyl-4-heptafluoropropyl-1,2-dihydropyrimidine (2l). Colorless oil. IR (film): 3260, 2980, 1632, 1542, 1230, 1184, 1120 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.75 (1H, d, J=5.7 Hz), 5.13 (1H, d, J=5.7 Hz), 4.20 (1H, br s), 1.95–1.61 (2H, m), 1.38 (3H, s), 0.92 (3H, t, J=6.2 Hz). ^{19}F NMR ($CDCl_3$): δ −80.6 (3F, m), −118.1 (2F, m), −127.7 (2F, m). EIMS (*m*/*z*, %): 277 (M^+−Me, 24), 265 (M^+−Et, 100). Anal. Calcd for $C_{10}H_{11}F_7N_2$: C, 41.10; H, 3.79; N, 9.58. Found: C, 40.97; H, 3.73; N, 9.46.

4.3.10. 2-Methyl-2-propyl-4-heptafluoropropyl-1,2-dihydropyrimidine (2m). White solid, mp: 48–50 °C. IR

(KBr): 3238, 3075, 2962, 1624, 1542, 1351, 1231, 1118, 895, 753 cm^{-1}. ^1H NMR ($CDCl_3$): δ 6.75 (1H, d, J=5.7 Hz), 5.13 (1H, d, J=5.7 Hz), 4.12 (1H, br s), 1.89–0.91 (10H, m). ^{19}F NMR ($CDCl_3$): δ −80.7 (3F, m), −117.1 (2F, m), −127.1 (2F, m). EIMS (*m/z*, %): 306 (M^+, 2), 291 (M^+-CH_3, 13), 263 ($M^+-C_3H_7$, 100). Anal. Calcd for $C_{11}H_{13}F_7N_2$: C, 43.14; H, 4.27; N, 9.14. Found: C, 42.86; H, 4.27; N, 9.03.

4.3.11. 2-Methyl-2-phenyl-4-heptafluoropropyl-1,2-dihydropyrimidine (2n). Oil. IR (film): 3398, 3284, 1627, 1537, 1351, 1230, 1120, 935, 765 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.27–7.55 (5H, m), 6.92 (1H, d, J=6.9 Hz), 5.33 (1H, d, J=6.9 Hz), 1.81 (3H, s). ^{19}F NMR ($CDCl_3$): δ −79.7 (3F, m), −116.4 (2F, m), −125.9 (2F, m). EIMS (*m/z*, %): 340 (M^+, 2), 325 (M^+-Me, 100). EI-HR calcd for $C_{13}H_8F_7N_2$: 325.0576. Found: 325.0560.

4.4. The isolation of 6[9]

A mixture of **3c** (1 mmol) and $ZnCl_2$ (1 mmol) in THF (10 mL) was stirred under ammonia atmosphere at 50 °C for 2 h. After cooling, 20 mL water was added and the solution was extracted with ethyl acetate (3×10 mL), the combined organic layer was washed with water and dried over anhydrous Na_2SO_4. After removal of solvent, the crude product was purified by column chromatography to give compound **6**. ^1H NMR ($CDCl_3$) δ: 9.49 (1H, br), 7.30–7.20 (1H, m), 6.27 (1H, br), 5.45 (1H, d, J=7.2 Hz). ^{19}F NMR ($CDCl_3$) δ: −77.9 (s).

4.5. The reaction of 6 with ammonia and 5a

A mixture of **6** (1 mmol) and $ZnCl_2$ (1 mmol) in THF (10 mL) was stirred under ammonia atmosphere for 2 h at room temperature. Then a solution of **5a** (1.5 mmol) in THF (10 mL) was added dropwise. The resulting mixture was stirred at 50 °C under ammonia atmosphere for a few hours (monitored by ^{19}F NMR). After cooling, 20 mL water was added and the solution was extracted with ethyl acetate (3×10 mL). The combined organic layer was washed with water and dried over anhydrous Na_2SO_4. After removal of solvent, the crude product was purified by column chromatography (ethyl acetate and petroleum ether) to give **2c**.

4.6. The preparation of 7

A mixture of **2** (10 mmol) and DDQ or TCBQ (15 mmol) in CH_2Cl_2 or acetonitrile (50 mL) was stirred at room temperature for 24 h. After removal of solvent, the crude product was purified by column chromatography to give **7**.

4.6.1. 2-Propyl-4-heptafluoropropylpyrimidine (7e).[10] Oil. ^1H NMR ($CDCl_3$): δ 8.67 (1H, d, J=4.8 Hz), 7.25 (1H, d, J=4.8 Hz), 2.74 (2H, t, J=7.5 Hz), 1.60–1.53 (2H, m, CH_2), 0.69 (3H, t, J=7.5 Hz). ^{19}F NMR ($CDCl_3$): δ −81.2 (3F, m), −117.4 (2F, m), −127.4 (2F, m).

4.6.2. 2-Propyl-4-(3-chloro-1,1,2,2,3,3-hexafluoropropyl)pyrimidine (7j).[9] Oil. ^1H NMR ($CDCl_3$): δ 8.91 (1H, d, J=4.8 Hz), 7.50 (1H, d, J=4.8 Hz), 2.72 (2H, t, J=7.5 Hz), 1.61–1.52 (2H, m), 0.69 (3H, t, J=7.5 Hz). ^{19}F NMR ($CDCl_3$): δ −66.8 (2F, m), −115.3 (2F, m), −121.4 (2F, m).

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References and notes

1. (a) Kanai, M.; Percy, J. M. *Tetrahedron Lett.* **2000**, *41*, 2453; (b) Mantani, T.; Shiomi, K.; Konno, T.; Ishihara, T.; Yamanaka, H. *J. Org. Chem.* **2001**, *66*, 3442; (c) Zhou, W.; Gumina, G.; Chong, Y.; Wang, J. N.; Schinazi, R. F.; Chu, C. K. *J. Med. Chem.* **2004**, *47*, 3399; (d) Schlosser, M.; Brugger, N.; Schmidt, W.; Amrhein, N. *Tetrahedron* **2004**, *60*, 7731.
2. (a) Goldmann, S.; Stoltefuss, J. *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 1559; (b) Kappe, C. *Tetrahedron* **1993**, *49*, 6937; (c) Rovnyak, G. C.; Kimball, S. D.; Beyer, B. *J. Med. Chem.* **1995**, *38*, 119.
3. (a) Traube, W.; Schwarz, R. *Chem. Ber.* **1899**, *32*, 3163; (b) Stoel, R. E.; Plas, H. C. *Recl. Trav. Chim. Pays-Bas* **1978**, *97*, 116; (c) Plas, H. C.; Charushin, V. N.; Veldhuizen, B. *J. Org. Chem.* **1983**, *48*, 1354; (d) Nishio, T.; Tokunaga, T.; Omote, Y. *Synth. Commun.* **1984**, *14*, 363; (e) Barluenga, J.; Pozo, C. D.; Olano, B. *Synthesis* **1996**, 133; (f) Fraley, M. E.; Hoffman, W. F.; Rubino, R. S.; Hungate, R. W.; Tebben, A. J.; Rutledge, R. Z.; McFall, R. C.; Huckle, W. R.; Kendall, R. L.; Coll, K. E.; Thomas, K. A. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2767.
4. (a) Okada, E.; Kinomura, T.; Takeuchi, H.; Hojo, M. *Heterocycles* **1997**, *45*, 339; (b) Okada, E.; Kinomura, T.; Higashiyama, Y. *Heterocycles* **1998**, *48*, 2347; (c) Zanatta, N.; Fagundes, M. B.; Ellensohn, R.; Marques, M.; Bonacorso, H. G.; Martins, M. A. P. *J. Heterocycl. Chem.* **1998**, *35*, 451; (d) Lin, Y.; Liu, J.-T.; Yang, X.-J. *Chin. J. Chem.* **2007**, *25*, 113.
5. Part of this work was published as a communication in Tetrahedron Letters: Yang, X.-J.; Liu, J.-T. *Tetrahedron Lett.* **2004**, *45*, 5305.
6. (a) Yang, X.-J.; Liu, J.-T.; Zhao, F.-L. *J. Fluorine Chem.* **2004**, *125*, 415; (b) Yang, X.-J.; Chen, M.-P.; Yuan, W.-J.; Liu, J.-T. *Huadong Ligong Daxue Xuebao (Chinese)* **2006**, *32*, 1440.
7. Crystallographic data (excluding structure factors) for the structure of **2a** in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 233537. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(0) 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk].
8. (a) Tang, X.-Q.; Hu, C.-M. *J. Chem. Soc., Perkin Trans. 1* **1994**, 2161; (b) Wang, Q.-F.; Mao, Y.-Y.; Qin, C.-Y.; Zhu, S.-Z.; Hu, C.-M. *Tetrahedron Lett.* **1998**, *39*, 2377; (c) Wang, Q.-F.; Hu, C.-M. *J. Fluorine Chem.* **1999**, *95*, 141.
9. Hojo, M.; Masuda, R.; Okada, E.; Sakaguchi, S.; Narumiya, H.; Morimoto, K. *Tetrahedron Lett.* **1989**, *30*, 6173.
10. Guan, H.-P.; Hu, C.-M. *Synthesis* **1996**, 997.