Available online at www.sciencedirect.com
ScienceDirect
Journal of Fluorine Chemistry 127 (2006) 1168–1174
JOURNAL OF FLUORINE CHEMISTRY
www.elsevier.com/locate/fluor

Facile synthesis of α-fluoro substituted amidines from imidoyl chlorides and some of its application

Yong-Ming Wu [a,*], Min Zhang [a,b], Yi-Qun Li [b,**]

[a] *Key Laboratory of Organofluorine Chemistry, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, 354 Fenglin Road, Shanghai 200032, China*

[b] *Department of Chemistry, Jinan University, Guangzhou 510632, PR China*

Received 7 April 2006; received in revised form 5 June 2006; accepted 6 June 2006
Available online 15 June 2006

Abstract

A series of α-fluoro subustituted amidines were synthesized from corresponding fluorinated imidoyl chlorides in good to excellent yields and some of its applications are outlined in our programs.

Keywords: α-Fluoro subustituted imidoyl chlorides; α-Fluoro subustituted amidines; Fluorinated benzoimidazole; Aryl amination; 1,4-Dihydropyridine; Fluorinated aminals

1. Intruduction

Amidines, the nitrogen analogues of carboxylic acids, are structural parts of numerous compounds of biological interest including important medical and biochemical agents. They are used as trypsin inhibitors [1], platelet fibrinogen receptor antagonists [2], VLA-4 antagonists [3], etc. Besides their role as a pharmacophore group in biologically active agents, amidines are also used as valuable intermediates for the preparation of heterocycles [4], e.g., β-lactams [5], imidazol [6], indole [7], and pyrimidine [8].

Numerous methods for the synthesis of amidines are reported [9], such as the widely used Pinner synthesis [10] and the reaction of imidoyl chloride with ammonia or primary or secondary amines [11]. However there are few reports on the synthesis of fluorinated arylamidines [12]. In the past few years organofluorine chemistry has returned as an expanding and productive area of research, as can be seen by the increasing number of recent publications, reviews, topics, and monographs [13]. Furthermore, organofluorine chemicals have found a wide range of applications in medicine and agriculture due, in part, to the unique biological properties imparted by the fluorine atom [14]. In search for new CF_2-containing reactive synthetic intermediates [15], we have found that bromodifluoroacetimidoyl halides showed unique properties compared with their non-fluorinated analogues because of the existence of $BrCF_2$ group. As the continue of the research, in this report, we would like to firstly describe a mild and novel protocol of preparing CF_2- and CF_3-containing amidines by the reaction of amines with fluoroacetimidoyl chlorides and some chemical transformation of the result fluorinated amidines.

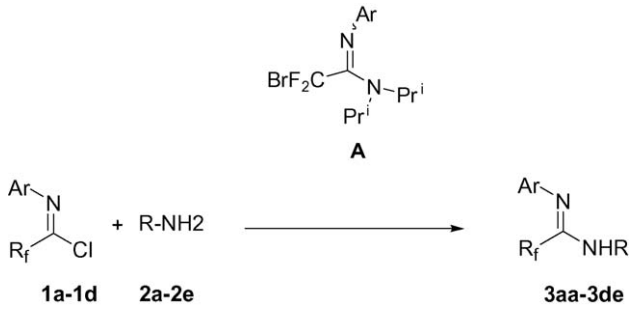
2. Results and discussion

During the course of our research on the Sonogashira reaction of bromodifluoroacetimidoyl halides with terminal alkynes [15d], it was found accidentally that when diisopropylamine was used as a base, a *N*-diisopropylamidines (**A**) was obtained in moderate yield, obviously this was the result of the nucleophilc substitution reaction of imidoyl chlorides with the secondary amine. Then we used different kind of amines to expand this reaction, the result was listed in Scheme 1 and Table 1.

In all cases studied, the nucleophilic substitution reaction proceeded smoothly to give the corresponding disubstituted amidines in good to excellent yields. It was interesting to find that different kind of amine had dramatically different reactivity in this transformation. Strong electron-withdrawing

* Corresponding author. Tel.: +86 21 54925190; fax: +86 21 64166128.
** Corresponding author.
E-mail address: ymwu@mail.sioc.ac.cn (Y.-M. Wu).

0022-1139/$ – see front matter © 2006 Elsevier B.V. All rights reserved.
doi:10.1016/j.jfluchem.2006.06.008

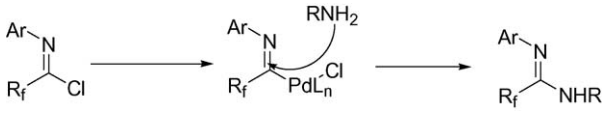


Scheme 1. The substitution reaction of imidoyl chlorides with amines.

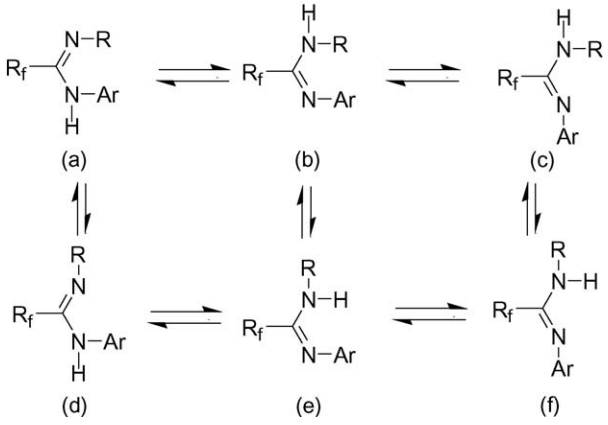
groups in *N*-aryl (e.g., F) of imidoyl chlorides would promote the reactions rates, and short reaction time was needed. On the other side, nucleophilic reagent with strong electron-withdrawing groups (e.g., $-NO_2$) would prolong the reaction time and the catalyst $PdCl_2(PPh_3)_2$ was needed (entries 3, 8, 13, 18), Usually, the reactions of aliphatic amine and ammonia (**2d**, **2e**) with imidoyl chlorides can proceed quickly under room temperature and the reaction could be completed within 5–30 min (entries 4, 5, 9, 10, 14, 15, 19, 20), while the substitution reactions of aromatic amines needed heating to 80 °C to obtain desired results.

Generally speeking, an addition–elimination route was involved in the active amine (i.e., Scheme 2).

But for unreactive amine, a palladium promoted coupling mechanism is more reasonable (i.e., Scheme 3).

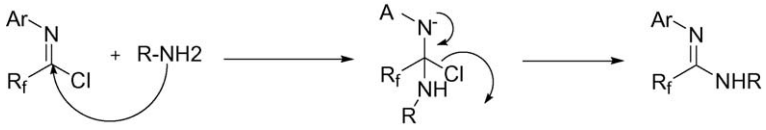


Scheme 3.



Scheme 4. Six possible isomers of *N*,*N*′-disubetituted amides.

There might be six isomers in the *N*,*N*′-disubstituted amidines (Scheme 4) [16]. Among them: **a** versus **b** and **d** versus **e** are tautomers; **a** versus **d**, **b** versus **c** and **e** versus **f** are *E*-, *Z*-isomer; **b** versus **e** and **c** versus **f** are rotamers. It was interesting to note that when *R* was not an aromatic group, there

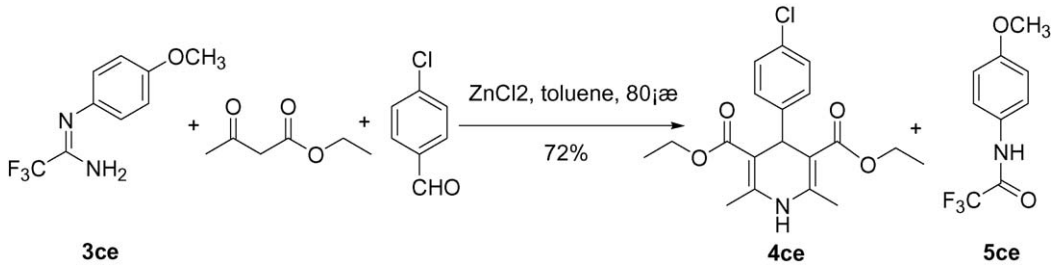


Scheme 2.

Table 1
Nucleophilic substitutions reaction of imidoyl chlorides with amines[a]

Entry	Ar (**1a–1d**)	R_f	R (**2a–2e**)	Time/temperature	**3aa–3gd**/yield (%)
1	3,4-2F–C_6H_3 (**1a**)	BrF_2C	4-CH_3O–C_6H_4 (**2a**)	1 h/80 °C	**3aa**/92
2	3,4-2F–C_6H_3 (**1a**)	BrF_2C	C_6H_5 (**2b**)	2 h/80 °C	**3ab**/88
3	3,4-2F–C_6H_3 (**1a**)	BrF_2C	4-NO_2–C_6H_4 (**2c**)	6 h/80 °C	**3ac**/60[a]
4	3,4-2F–C_6H_3 (**1a**)	BrF_2C	*n*-C_4H_9 (**2d**)	5 min/room temperature	**3ad**/98
5	3,4-2F–C_6H_3 (**1a**)	BrF_2C	NH_3 (**2e**)	30 min/room temperature	**3ae**/92
6	3,4-2F–C_6H_3 (**1b**)	F_3C	4-CH_3O–C_6H_4 (**2a**)	30 min/80 °C	**3ba**/98
7	3,4-2F–C_6H_3 (**1b**)	F_3C	C_6H_5 (**2b**)	1 h/80 °C	**3bb**/96
8	3,4-2F–C_6H_3 (**1b**)	F_3C	4-NO_2–C_6H_4 (**2c**)	4 h/80 °C	**3bc**/66[a]
9	3,4-2F–C_6H_3 (**1b**)	F_3C	*n*-C_4H_9 (**2d**)	5 min/room temperature	**3bd**/92
10	3,4-2F–C_6H_3 (**1b**)	F_3C	NH_3 (**2e**)	30 min/room temperature	**3be**/96
11	4-CH_3O–C_6H_4 (**1c**)	F_3C	4-CH_3O–C_6H_4 (**2a**)	4 h/80 °C	**3ca**/85
12	4-CH_3O–C_6H_4 (**1c**)	F_3C	C_6H_5 (**2b**)	5 h/80 °C	**3cb**/73
13	4-CH_3O–C_6H_4 (**1c**)	F_3C	4-NO_2–C_6H_4 (**2c**)	8 h/80 °C	**3cc**/52[a]
14	4-CH_3O–C_6H_4 (**1c**)	F_3C	*n*-C_4H_9 (**2d**)	5 min/room temperature	**3cd**/96
15	4-CH_3O–C_6H_4 (**1c**)	F_3C	NH_3 (**2e**)	30 min/room temperature	**3ce**/83
16	4-CH_3O–C_6H_4 (**1d**)	BrF_2C	4-CH_3O–C_6H_4 (**2a**)	5 h/80 °C	**3da**/80
17	4-CH_3O–C_6H_4 (**1d**)	BrF_2C	C_6H_5 (**2b**)	5 h/80 °C	**3db**/71
18	4-CH_3O–C_6H_4 (**1d**)	BrF_2C	4-NO_2–C_6H_4 (**2c**)	8 h/80 °C	**3dc**/61[a]
19	4-CH_3O–C_6H_4 (**1d**)	BrF_2C	*n*-C_4H_9 (**2d**)	5 min/room temperature	**3dd**/93
20	4-CH_3O–C_6H_4 (**1d**)	BrF_2C	NH_3 (**2e**)	30 min/room temperature	**3de**/92

[a] $PdCl_2(PPh_3)_2$ was used as catalyst.



Scheme 5. Synthesis of 1,4-dihydropyridine.

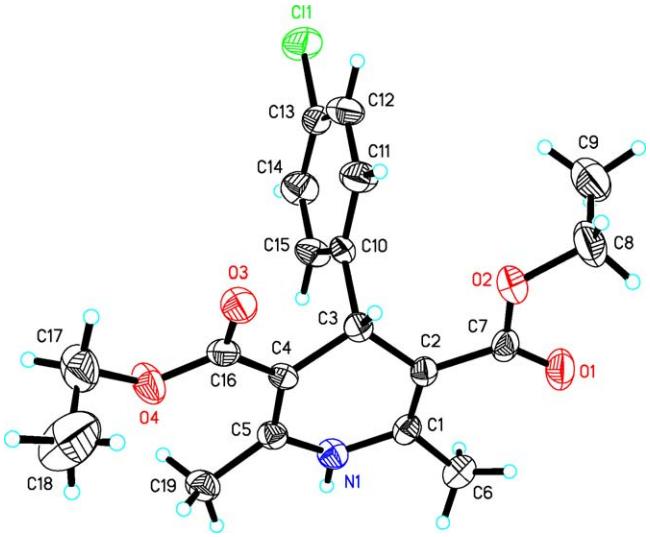
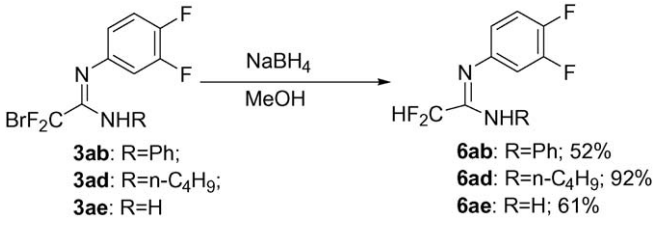


Fig. 1. Crystal structure of 1,4-dihydropyridine.

were only two isomers were detected in ^{19}F NMR spectra, while if *R* was an aromatic group, four isomers were found. Obviously this was due to the conjugated effects of the aromatic group. These results also mean that because of low energy difference between the rotamers, they could not be detected in this amidine at room temperature.

With the fluorinated amidines in hand, we started to look at the various chemical transformation that this kind of amidines undergo. Hantzsch three components synthesis is a versatile method for the synthesis of 1,4-dihydropyridine [17]. It was found that if this fluorinated amidine was used as one component to perform the same reaction, under catalysis with $ZnCl_2$ and refluxing in toluene for 3 h, a 1,4-dihydropyridine **5** could also be synthesized in 72% yield (Scheme 5). The structure of pyridine was confirmed by X-ray (Fig. 1) [18].

Attempts to transfer the amidines to the corresponding ketene Aminals by reducing with $NaBH_4$ was not succeeded, an unexpected products were obtained. It was found that when



Scheme 6.

3ab, **3ad**, **3ae** reacted wtih sodium borohydride in methanol, the CF_2Br group in amidines was converted into CF_2H-containing amidines **6**, and with no reaction for CF_3-containing amidines (Scheme 6).

3. Conclusion

In conclusion, a series of bromodifluoromethylated and trifluoromethylated amidnes were synthesized by the reaction of *N*-arylbromodifluoroacetimidoyl chloride or *N*-aryltrifluoroacet-imidoyl chloride with amines under mild conditions. These products could be used to construct different kinds of containing bromodifluoromethyl and trifluoromethyl heterocycles. Further study on this subject is in progress.

4. Experimental

Unless otherwise noted, solvents and reagents were commercial available and used as received. ^1H NMR spectra were recorded on a Brucker AM-300 (300 MHz) spectrometer with Me_4Si as internal standard. ^{19}F NMR spectra were taken on Brucher AM-300 (282 MHz) spectrometer with $CFCl_3$ as external standard, downfield shifts being designed as positive. Mass spectra were taken on a HP 5989a spectrometer, while elemental analysis were performed by this institute.

*4.1. General procedure for the synthesis 2-bromo-N-(3,4-difluoro-phenyl)-2,2-difluoro-N′-(4-methoxy)-acetamidine (**3aa**)*

To a stirred mixture of K_2CO_3 (138 mg, 1 mmol) in toluene, 2-bromo-*N*-(3,4-difluoro-phenyl)-2,2-difluoro-acetimidoyl chloride (**1a**, 305 mg, 1 mmol) and 4-methoxy-phenylamine (**2a**, 135 mg, 1.1 mmol) were added successively. The mixture was stirred at 80 °C for 1 h and then filtered, washed by ethyl ether. After removing the solvent under reduced pressure the crude product was purified by column chromatography on silica gel [eluent:ethyl acetate/petroleum ether (b.p. 60–90), 1:5] to give the product (**3aa**, 360 mg, 92%).

*4.2. General procedure for the synthesis of 2-bromo-N-butyl-N′-(3,4-difluoro-phenyl)-2,2-difluoro-acetamidine (**3ad**)*

To a stirred mixture of 2-bromo-*N*-(3,4-difluoro-phenyl)-2,2-difluoro-acetimidoyl chloride (**1a**, 305 mg, 1 mmol) in

toluene, butylamine (**2d**, 183 mg, 2.5 mmol) was added. The mixture was stirred at room temperature for 5 min and then filtered, washed by ethyl ether, after removing the solvent under reduced pressure, the product (**3ad**, 334 mg, 98%) was obtained without any further purification.

*4.3. General procedure for the synthesis of 2-bromo-N-(3,4-difluoro-phenyl)-2,2-difluoro-acetamidine (**3ae**)*

To a stirred mixture of 2-bromo-*N*-(3,4-difluoro-phenyl)-2,2-difluoro-acetimidoyl chloride (**1a**, 305 mg, 1 mmol) in toluene, the gas of ammonia was aerated. The mixture was stirred at room temperature for 30 min and then filtered, washed by ethyl ether, after removing the solvent under reduced pressure, the product (**3ae**, 263 mg, 98%) was obtained without any further purification.

*4.3.1. 2-Bromo-2,2-difluoro-N-(4-methoxyl-phenyl)-N′-3,4-difluorophenyl-acetamdine (**3aa**)*

White solid. m.p.: 80–83 °C. ^{1}H NMR: δ 6.59–6.96 (m, 8H), 3.82 (s, 3H). ^{19}F NMR: δ −51.06 (s):−51.06 (s):−51.06 (s):−56.76 (s) = 1:1:3:3, −138.51 to −138.41 (m, 1F), −145.10 to 145.06 (m, 1F). IR (film, cm^{-1}): 3427, 3291, 2839, 1680, 1600, 1417, 1378, 1254, 1166, 862, 826; *m/z* (EI) 390 (36), 261 (69), 139 (12), 122 (65), 113 (19). Calc. for $C_{15}H_{11}BrF_4N_2O$: C, 46.06; H, 2.83; N, 7.16. Found: C, 46.17; H, 2.88; N, 6.92.

*4.3.2. 2-Bromo-2,2-difluoro-N-phenyl-N′-3,4-difluorophenyl-acetamdine (**3ab**)*

White solid. m.p.: 61–63 °C. ^{1}H NMR: δ 6.81–7.26 (m, 4H), 6.46–6.75 (m, 5H), 6.45 (s, 1H). ^{19}F NMR: δ −51.10 (s):−56.15 (s):−62.28 (s):−62.36 (s) = 1:1:3:3, −143.48 to −143.28 (m, 1F), −149.34 to −148.99 (m, 1F). IR (film, cm^{-1}): 3428, 1679, 1596, 1417, 1510, 1393, 1246, 1173, 1084, 872; *m/z* (EI) 360 (40), 231 (84), 139 (22), 113 (20), 92 (67), 77 (100). Calc. for $C_{14}H_9BrF_4N_2$: C, 46.56; H, 2.51; N, 7.76. Found: C, 46.77; H, 2.68; N, 7.72.

*4.3.3. 2-Bromo-2,2-difluoro-N-(4-nitro-phenyl)-N′-3,4-difluorophenyl-acetamdine (**3ac**)*

Yellow solid. m.p.: 114–117 °C. ^{1}H NMR: δ 8.12–8.20 (d, J = 10.83, 2H), 7.72–7.84 (m, 2H), 7.09–7.26 (m, 2H), 6.59–6.98 (m, 2H). ^{19}F NMR: δ −53.20 to −51.78 (m, 2F) −137.43 to −137.41 (m, 1F), −141.66 to 140.83 (m, 1F). IR (film, cm^{-1}): 3372, 2924, 2853, 1681, 1591, 1513, 1370, 1249, 1174, 877, 856; *m/z* (EI) 405 (36), 276 (100), 139 (27), 113 (32). Calc. for $C_{14}H_8BrF_4N_3O_2$: C, 41.40; H, 1.99; N, 10.35. Found: C, 41.71; H, 2.16; N, 10.16.

*4.3.4. 2-Bromo-2,2-difluoro-N-butyl-N′-3,4-difluorophenyl-acetamdine (**3ad**)*

Oil. ^{1}H NMR: δ 7.03 (d, J = 9.03 Hz, 1H), 6.68 (t, J = 9.15 Hz, 1H), 6.54 (t, J = 7.80 Hz, 1H), 3.18–3.29 (m, 2H), 1.25–1.46 (m, 4H), 0.93 (m, 3H). ^{19}F NMR: δ −50.36 (s):−55.18 (s) = 2:1, −138.32 to −136.56 (m, 1F), −147.08 to 144.96 (m, 1F). IR (neat, cm^{-1}): 3462, 2962, 1667, 1600, 1510, 1425, 1253, 1207, 1114, 967, 909, 829; *m/z* (EI) 340 (68), 261 (42), 211 (12), 139 (20), 113 (21). Calc. for $C_{12}H_{13}BrF_4N_2$: C, 42.25; H, 3.84; N, 8.21. Found: C, 42.28; H, 3.88; N, 8.16.

*4.3.5. 2-Bromo-2,2-difluoro-N-3,4-difluorophenyl-acetamdine (**3ae**)*

White solid. m.p.: 90–91 °C. ^{1}H NMR: δ 7.20 (d, J = 9.30 Hz, 1H), 6.79 (t, J = 9.30 Hz, 1H), 6.65 (t, J = 8.10 Hz, 1H), 4.93 (s, 2H), 3.18–3.29 (m, 2H), 1.25–1.46 (m, 4H), 0.93 (m, 3H). ^{19}F NMR: δ −57.36 (s, 2F), −135.26 to −135.16 (m, 1F), −143.29 to 143.16 (m, 1F). IR (film, cm^{-1}): 3475, 2978, 1682, 1601, 1513, 1478, 1397, 1257, 1210, 1036, 956, 926, 871, 851, 825; *m/z* (EI) 284 (15), 155 (42), 139 (3), 113 (36). Calc. for $C_8H_5BrF_4N_2$: C, 33.71; H, 1.77; N, 9.83. Found: C, 33.91; H, 1.79; N, 9.62.

*4.3.6. 2,2,2-Trifluoro-N-(4-methoxyl-phenyl)-N′-3,4-difluorophenyl-acetamdine (**3ba**)*

White solid. m.p.: 114–116 °C. ^{1}H NMR: δ 7.46–7.52 (m, 1H), 6.74–7.06 (m, 4H), 6.41–6.59 (m, 3H), 3.69–3.76 (d, 3H). ^{19}F NMR: δ −63.78 (s):−63.87 (s):−70.13 (s):−70.46 (s) = 2:4:1:4, −137.71 to −137.37 (m, 1F), −146.08 to 146.05 (m, 1F). IR (film, cm^{-1}): 3361, 1673, 1597, 1554, 1508, 1417, 1360, 1285, 1245, 1184, 1027, 974, 865, 821; *m/z* (EI) 329 (88), 261 (15), 208 (46), 139 (5), 113 (88). Calc. for $C_{15}H_{11}F_5N_2O$: C, 54.55; H, 3.36; N, 8.48. Found: C, 54.60; H, 3.43; N, 8.49.

*4.3.7. 2,2,2-Trifluoro-N-phenyl-N′-3,4-difluorophenyl-acetamdine (**3bb**)*

Yellowish solid. m.p.: 70–72 °C. ^{1}H NMR: δ 7.54–7.64 (m, 1H), 7.20–7.36 (m, 3H), 7.05–7.10 (m, 4H), 6.47–6.56 (m, 1H). ^{19}F NMR: δ −63.78 (s):−63.90 (s):70.03 (s):−70.15 (s) = 5:5:1:4, −137.54 to −136.16 (m, 1F), −145.86 to 143.96 (m, 1F). IR (neat, cm^{-1}): 3238, 3061, 1679, 1598, 1552, 1510, 1425, 1342, 1259, 1151, 1028, 976, 864, 815; *m/z* (EI) 300 (100), 231 (17), 208 (24), 113 (23). Calc. for $C_{14}H_9F_5N_2$: C, 56.01; H, 3.02; N, 9.33. Found: C, 56.04; H, 3.15; N, 9.32.

*4.3.8. 2,2,2-Trifluoro-N-(4-nitro-phenyl)-N-3,4-difluorophenyl-acetamdine (**3bc**)*

Yellow solid. m.p.: 140–142 °C. ^{1}H NMR: δ 8.17–8.22 (m, 2H), 7.82–7.86 (m, 1H), 7.65–7.73 (m, 1H), 7.20–7.34 (m, 3H), 6.57–6.96 (m, 1H). ^{19}F NMR: δ −63.79 (s):−63.90 (s):64.72 (s):−64.82 (s) = 3:3:5:5, −134.54 to −134.43 (m, 1F), −144.47 to 144.40 (m, 1F). IR (film, cm^{-1}): 3370, 1681, 1593, 1512, 1443, 1339, 1266, 1159, 1105, 969, 855, 814; *m/z* (EI) 344 (69), 276 (21), 208 (63), 113 (100). Calc. for $C_{14}H_8F_5N_3O_2$: C, 48.71; H, 2.34; N, 12.17. Found: C, 48.79; H, 2.41; N, 12.11.

*4.3.9. 2,2,2-Trifluoro-N-butyl-N′-3,4-difluorophenyl-acetamdine (**3bd**)*

Colorless oil. ^{1}H NMR: δ 7.26–7.28 (m, 1H), 6.50–6.63 (m, 2H), 5.15 (s, 1H), 3.02–3.34 (m, 2H), 1.19–1.44 (m, 4H), 0.97 (m, 3H). ^{19}F NMR: δ −64.46 (s):−70.67 (s) = 3:1, −138.09 to

−136.13 (m, 1F), −146.56 to −144.54 (m, 1F). IR (neat, cm^{-1}): 3470, 2965, 1688, 1601, 1514, 1425, 1382, 1126, 1101, 959, 867, 817; *m/z* (EI) 280 (13), 223 (62), 208 (45), 113 (72). Calc. for $C_{12}H_{13}F_5N_2$: C, 51.43; H, 4.68; N, 10.00. Found: C, 51.44; H, 4.86; N, 9.87.

*4.3.10. 2,2,2-Trifluoro-N-3,4-difluorophenyl-acetamdine (**3be**)*

White solid. m.p.: 70–72 °C. ^{1}H NMR: δ 7.11–7.26 (m, 1H), 6.74–6.81 (m, 1H), 6.62–6.68 (m, 1H), 5.01 (s, 2H). ^{19}F NMR: δ −73.26 (s, 1H), −135.27 to −135.12 (m, 1F), −143.26 to −143.11 (m, 1F). IR (film, cm^{-1}): 3467, 2961, 1669, 1611, 1512, 1429, 1273, 1227, 1164, 969, 909, 829; *m/z* (EI) 224 (62), 155 (100), 113 (55). Calc. for $C_8H_5F_5N_2$: C, 42.87; H, 2.25; N, 12.50. Found: C, 42.92; H, 2.23; N, 12.61.

*4.3.11. 2,2,2-Trifluoro-N-4-methoxyphenyll-N′-4-mehtoxylphenyl-acetamdine (**3ca**)*

White solid. m.p.: 83–86 °C. ^{1}H NMR: δ 6.76–6.84 (m, 2H), 6.41–6.60 (m, 5H), 6.44–6.48 (d, 1H), 3.67–3.74 (d, 6H). ^{19}F NMR: δ −63.68 (s):−68.89 (s) = 2:3. IR (film, cm^{-1}): 3354, 2839, 1668, 1504, 1466, 1415, 1247, 1180, 1034, 918, 827; *m/z* (EI) 324 (100), 202 (87), 133 (7), 122 (59). Calc. for $C_{16}H_{15}F_3N_2O_2$: C, 59.26; H, 4.66; N, 8.64. Found: C, 59.40; H, 4.63; N, 8.53.

*4.3.12. 2,2,2-Trifluoro-N-phenyl-N′-4-mehtoxylphenyl-acetamdine (**3cb**)*

Yellowish oil. ^{1}H NMR: δ 7.55–7.65 (m, 1H), 7.31–7.36 (m, 1H), 7.06–7.11 (m, 2H), 6.94–6.99 (m, 5H), 6.62–6.72 (m, 1H), 3.76 (s, 3H). ^{19}F NMR: δ −63.71 (s):−63.77 (s):−68.87 (s):69.80 (s) = 2:1:2:1. IR (film, cm^{-1}): 3647, 1678, 1596, 1510, 1400, 1338, 1246, 1147, 1033, 829; *m/z* (EI) 294 (34), 225 (11), 202 (16), 122 (30). Calc. for $C_{15}H_{13}F_3N_2O$: C, 61.22; H, 4.45; N, 9.52. Found: C, 61.35; H, 4.44; N, 9.37.

*4.3.13. 2,2,2-Trifluoro-N-4-nitrophenyl-N′-4-mehtoxylphenyl-acetamdine (**3ca**)*

Yellow solid. m.p.: 100–102 °C.^{1}H NMR: δ 8.04–8.07 (d, *J* = 7.5 Hz, 2H), 7.21–7.26 (m, 1H), 6.91 (s, 1H), 6.77–6.85 (m, 5H), 3.74–3.76 (d, 3H). ^{19}F NMR: δ −63.67 (s):−63.77 (s):71.24 (s):75.62 (s) = 3:3:2:1. IR (film, cm^{-1}): 3373, 2839, 1680, 1590, 1510, 1417, 1342, 1249, 1107, 1032, 916, 853, 830; *m/z* (EI) 339 (60), 202 (64), 122 (100). Calc. for $C_{15}H_{13}F_3N_2O$: C, 53.10; H, 3.57; N, 12.39. Found: C, 53.15; H, 3.66; N, 12.39.

*4.3.14. 2,2,2-Trifluoro-N-butyl-N′-4-mehtoxylphenyl-acetamdine (**3cd**)*

Colorless oil. ^{1}H NMR: δ 6.70–6.89 (m, 4H), 4.60 (s):4.58 (s) = 1:1, 3.77 (s):3:78 (s) = 1:1, 3.32 (dd, *J* = 6.9 Hz):3.06 (dd, *J* = 6.9 Hz) = 1:1, 1.60–1.67 (m):1.18–1.26 (m) = 1:1, 1.33–1.46 (m, 2H), 0.94–0.99 (t, *J* = 7.5 Hz):0.82–0.87 (t, *J* = 7.5 Hz) = 1:1. ^{19}F NMR: δ −64.23 (s):−70.08 (s) = 1:1. IR (neat, cm^{-1}): 3386, 2959, 2875, 1678, 1504, 1466, 1442, 1380, 1242, 1131, 1104, 1036, 892, 836; *m/z* (EI) 274 (29), 217 (27), 202 (29), 133 (30), 122 (44). Calc. for $C_{13}H_{17}F_3N_2O$: C, 56.93; H, 6.25; N, 10.21. Found: C, 56.87; H, 6.21; N, 10.19.

*4.3.15. 2,2,2-Trifluoro-N-4-methoxylphenyl-acetamdine (**3ce**)*

White solid. m.p.: 127–128 °C. ^{1}H NMR: δ 6.92 (d, *J* = 9.9 Hz, 2H), 6.88 (d, *J* = 9.9 Hz, 2H), 4.91 (s, 2H), 3.80 (s, 3H). ^{19}F NMR: δ −73.14 (s, 3F). IR (film, cm^{-1}): 3379, 2839, 1659, 1505, 1433, 1442, 1302, 1237, 1180, 1135, 1031, 860, 803; *m/z* (EI) 218 (100), 202 (34), 149 (90), 122 (9). Calc. for $C_9H_9F_3N_2O$: C, 49.55; H, 4.16; N, 12.84. Found: C, 49.67; H, 4.16; N, 12.77.

*4.3.16. 2-Bromo-2,2-difluoro-N-4-methoxylphenyl-N′-4-methoxylphenyl-acetamdine (**3da**)*

Yellow solid. m.p.: 132–134 °C. ^{1}H NMR: δ 7.46 (s, 1H), 6.84–6.96 (m, 4H), 6.46–6.78 (m, 4H), 3.81 (s):3.85 (s) = 1:1. ^{19}F NMR: δ −50.15 (s):−54.76 (s) = 1:3. IR (film, cm^{-1}): 3380, 2836, 1658, 1504, 1433, 1465, 1442, 1291, 1240, 1145, 1090, 1034, 957, 878, 826; *m/z* (EI) 385 (33), 255 (78), 133 (30), 122 (100). Calc. for $C_{16}H_{15}BrF_2N_2O_2$: C, 49.89; H, 3.92; N, 7.27. Found: C, 50.13; H, 4.16; N, 7.04.

*4.3.17. 2-Bromo-2,2-difluoro-N-phenyl-N′-4-methoxylphenyl-acetamdine (**3db**)*

Yellow solid. m.p.: 92–93 °C. ^{1}H NMR: δ 6.90–7.25 (m, 4H), 6.54–6.77 (m, 6H), 3.73 (m, 3H). ^{19}F NMR: δ −50.54 (s):−54.71 (s):55.69 (s):55.74 (s) = 2:2:1:1. IR (film, cm^{-1}): 3315, 2837, 1663, 1595, 1511, 1444, 1240, 1146, 1092, 1034, 957, 874; *m/z* (EI) 355 (100), 262 (12), 225 (58), 133 (11), 122 (73). Calc. for $C_{15}H_{13}BrF_2N_2O$: C, 50.72; H, 3.69; N, 7.89. Found: C, 50.89; H, 3.82; N, 7.74.

*4.3.18. 2-Bromo-2,2-difluoro-N-4nitrophenyl-N′-4-methoxylphenyl-acetamdine (**3dc**)*

White solid. m.p.: 112–115 °C. ^{1}H NMR: δ 7.99–8.03 (m, 2H), 7.12–7.25 (m, 2H), 6.71–6.83 (m, 5H), 3.72 (s):3.73 (s) = 2:1. ^{19}F NMR: δ −52.91 (s):−60.33 (s) = 1:2. IR (film, cm^{-1}): 3370, 2837, 1674, 1587, 1511, 1336, 1245, 1172, 1096, 1032, 957, 882, 830; *m/z* (EI) 400 (25), 270 (42), 133 (10), 122 (100). Calc. for $C_{15}H_{12}BrF_2N_3O_3$: C, 45.02; H, 3.02; N, 10.50. Found: C, 45.23; H, 3.36; N, 10.33.

*4.3.19. 2-Bromo-2,2-difluoro-N-butyl-N′-4-methoxylphenyl-acetamdine (**3dd**)*

Colorless oil. ^{1}H NMR: δ 6.72–6.92 (m, 4H), 4.88 (s):4.62 (s) = 2:3, 3.77 (s):3.78 (s) = 2:3, 3.33 (m):2.97 (m) = 2:3, 1.11–1.38 (m, 4H), 0.75–0.92 (m, 3H). ^{19}F NMR: δ −49.88 (s):−54.34 (s) = 2:3. IR (neat, cm^{-1}): 3382, 2959, 2873, 1661, 1503, 1466, 1239, 1178, 1104, 1035, 958, 915, 851; *m/z* (EI) 334 (32), 255 (38), 205 (27), 133 (35). Calc. for $C_{13}H_{17}BrF_2N_2O$: C, 46.58; H, 5.11; N, 8.36. Found: C, 46.81; H, 5.35; N, 8.22.

*4.3.20. 2-Bromo-2,2-difluoro-N-4-methoxylphenyl-acetamdine (**3de**)*

White solid. m.p.: 97–99 °C. ^{1}H NMR: δ 6.88–6.91 (m, 4H), 4.89 (s, 1H), 3.78 (s):3.80 (s) = 2:3. ^{19}F NMR: δ −56.80 (s):−56.81 (s) = 3:2. IR (film, cm^{-1}): 3333, 2837, 1669, 1608, 1446, 1442, 1380, 1289, 1240, 1179, 1107, 1032, 921, 852; *m/z*

(EI) 278 (25), 149 (100), 133 (9). Calc. for $C_9H_9BrF_2N_2O$: C, 38.73; H, 3.25; N, 10.04. Found: C, 38.93; H, 3.20; N, 10.03.

*4.4. General procedure for the synthesis of 1,4-dihydropyridine (**4**)*

A mixture of 4-chlorobenaldehyde (1.1 mmol), amidine (1 mmol), ethyl acetoacetate (1.2 mmol), $ZnCl_2$ (0.1 mmol) and toluene (2 mL) was stirred at 80 °C for 2 h. Then stopped the reaction, filtrated, the solid part was washed with ether. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography with 5:1 petroleum ether and ethyl acetate as eluent affording the product **4**.

*4.4.1. 4-(4-Chlorophenyl)-2,6-dimethyl-1,4-dihydropyridine-3,5-dicarboxylic acid diethyl ester (**4ce**)*

Yellowish solid. ^{1}H NMR: δ 7.14–7.23 (m, 4H), 5.69 (s, 1H), 4.95 (s, 1H), 4.03–4.14 (m, 4H), 2.32 (s, 6H), 1.22 (t, J = 7.2 Hz, 6H). IR (film, cm^{-1}): 3340, 2981, 1681, 1657, 1623, 1368, 1302, 1275, 1214, 1170, 1120, 1099, 1016, 912; *m/z* (EI) 363 (2), 252 (100), 224 (23), 196 (34).

4.5. General procedure for the for the reduction of amidine with $NaBH_4$

To a stirred solution of amidine (1 mmol) and $NaBH_4$ (40 mmol), methanol (20 mL) was added slowly. After addition, the mixture was stirred at room temperature for 8 h. Then stopped the reaction, filtrated, the solid part was washed with ether. After removal of the solvent under reduced pressure, the residue was purified by flash chromatography with 20:1 petroleum ether and ethyl acetate as eluent affording the product **6**.

*4.5.1. 2,2-Difluoro-N-phenyl-N′-3,4-difluorophenyl-acetamdine (**6ab**)*

Yellowish oil. ^{1}H NMR: δ 6.83–7.28 (m, 3H), 6.47–6.85 (m, 5H), 6.48–6.53 (m, 1H), 6.05 (td, J = 2.4 Hz, 1H). ^{19}F NMR: δ −121.96 (d, J = 54.62 Hz, 2F), −135.89 to −135.76 (m, 1F), −145.72 to −145.61 (m, 1F). IR (neat, cm^{-1}): 3438, 2927, 1657, 1597, 1509, 1367, 1335, 1209, 1151, 1110, 1037, 869; *m/z* (EI) 282 (47), 190 (44), 140 (49), 113 (100). Calc. for $C_{14}H_{10}F_4N_2$: C, 59.58; H, 3.57; N, 9.93. Found: C, 59.66; H, 3.69; N, 10.02.

*4.5.2. 2,2-Difluoro-N-butyl-N′-3,4-difluorophenyl-acetamdine (**6ad**)*

Yellowish oil. ^{1}H NMR: δ 6.98–7.08 (m, 1H), 6.62–6.68 (m, 1H), 6.49–6.52 (m, 1H), 6.06 (t, d, J = 2.4 Hz, 1H), 5.09 (m, 2H), 3.32–3.35 (m, 2H), 1.57–1.66 (m, 2H), 1.38–1.48 (m, 2H), 0.96–0.99 (m, 3H). ^{19}F NMR: δ −120.97 (d, J = 54.71 Hz, 2F), −136.99 to −136.84 (m, 1F), −145.97 to −145.86 (m, 1F). IR (neat, cm^{-1}): 3460, 2936, 2865, 1660, 1600, 1510, 1365, 1206, 1165, 1114, 1050, 868, 820; *m/z* (EI) 262 (52), 205 (69), 190 (44), 140 (60), 113 (41). Calc. for $C_{12}H_{14}F_4N_2$: C, 54.96; H, 5.38; N, 10.68. Found: C, 54.97; H, 5.42; N, 10.54.

*4.5.3. 2-Bromo-2,2-difluoro-N-3,4-difluorophenyl-acetamdine (**6ae**)*

Yellowish oil. ^{1}H NMR: δ 7.08–7.19 (m, 1H), 6.72–6.80 (m, 1H), 6.62–6.66 (m, 1H), 6.06 (td, J = 3.3 Hz, 1H), 4.86 (m, 2H). ^{19}F NMR: δ −122.38 (dd, J = 3.36 Hz, 2F), −135.57 to −135.49 (m, 1F), −143.81 to −143.72 (m, 1F). IR (neat, cm^{-1}): 3490, 1675, 1602, 1511, 1415, 1341, 1294, 1255, 1210, 1165, 1050, 955, 870, 824; *m/z* (EI) 206 (28), 190 (18), 140 (85), 113 (70). Calc. for $C_8H_6F_4N_2$: C, 46.61; H, 2.93; N, 13.59. Found: C, 46.73; H, 2.99; N, 13.40.

Acknowledgment

The authors thank the National Natural Science Foundation of China (NNSFC) (no. 20472104 and 20532040) for financial support.

References

[1] For some recent examples, see:
(a) C.-B. Xue, J. Roderick, S. Jackson, M. Rafalski, A. Rockwell, S. Mousa, R.E. Olson, W.F. DeGrado, Bioorg. J. Med. Chem. 5 (1997) 693–705;
(b) B.K. Blackburn, A. Lee, M. Baier, B. Kohl, A.G. Olivero, R. Matomoros, K.D. Robarge, R.S. McDowell, J. Med. Chem. 40 (1997) 717–729;
(c) D.S. Jackson, S.A. Fraser, L.-M. Ni, C.-M. Kam, U. Winkler, D.A. Johnson, C.J. Froelich, D. Hudig, J.C. Powers, J. Med. Chem. 41 (1998) 2289–2301.

[2] (a) B. Gabriel, M.T. Stubbs, A. Bergner, J. Hauptmann, W. Bode, J. Stürzebecher, L. Moroder, J. Med. Chem. 41 (1998) 4240–4250;
(b) K. Okumura, T. Shimazaki, Y. Aoki, H. Yamashita, E. Tanaka, S. Banba, K. Yazawa, K. Kibayashi, H. Banno, J. Med. Chem. 41 (1998) 40364052;
(c) H. Koshio, F. Hirayama, T. Ishihara, H. Kaizawa, T. Shigenaga, Y. Taniuchi, K. Sato, Y. Moritani, Y. Iwatsuki, T. Uemura, S. Kaku, T. Kawasaki, Y. Matsumoto, S.I. Sakamoto, S. Tsukamoto, Bioorg. Med. Chem. 12 (20) (2004) 5415–5426.

[3] T.M. Kamenecka, Y.-J. Park, L.S. Lin, S. de Laszlo, E.D. McCauley, G. Van Riper, L. Egger, U. Kidambi, R.A. Mumford, S. Tong, W. Tang, A. Colletti, Y. Teffera, R. Stearns, M. MacCoss, J.A. Schmidt, W.K. Hagmann, Bioorg. Med. Chem. Lett. 14 (9) (2004) 23232326.

[4] G.V. Boyd, Reactions and synthetic uses of amidines, in: S. Patai, Z. Rappoport (Eds.), The Chemistry of Amidines and Imidates, vol. 2, John Wiley & Sons, New York, 1991, pp. 367–415.

[5] K. Thiagarajan, V.G. Puranik, A.R.A.S. Deshmukh, B.M. Bgawak, Tetrahedron 56 (2000) 7811–7816.

[6] (a) B. Li, K.F. Charles, F. Richard, J.M. Hank, R. Joshua, T. Harry, Org. Process Res. Dev. 6 (2002) 682–683;
(b) E.M. Beccalli, A. Contini, P. Trimarco, Eur. J. Org. Chem. 20 (2003) 3976–3984.

[7] J. Renata, S. Jurij, S. Branko, G. Amalija, Tetrahedron 60 (2004) 4601–4608.

[8] (a) J.J. Cesar, J. Com. Chem. 7 (2005) 517–519;
(b) M.C. Bagley, D.D. Hughes, P.H. Taylor, Synlett 2 (2003) 259–261;
(c) C.B. Geraldine, C. Shannon, M. Zhang, C. Andrea, A. Robert, P. Ian, Tetrahedron Lett. 44 (2003) 3659–3662;
(d) S.K. Alexei, M. Eugen, R. Frank, J.J.M. Thomas, Angew. Chem. Int. Ed. 44 (2005) 6951–6956.

[9] (a) P.J. Dunn, Amidines and *N*-substituted amidines, Compr. Org. Funct. Group Transform. II 5 (2005) 655–689;
(b) G.V. Boyd, Recent advances in the synthesis of amidines, in: S. Patai, Z. Rappoport (Eds.), The Chemistry of Amidines and Imidates, vol. 2, John Wiley & Sons, New York, 1991, pp. 339–366.

[10] Z.W. Yin, Z.X. Zhang, J.L. Zhu, H. Wong, J.F. Kadow, Tetrahedron Lett. 46 (2005) 4919–4923.
[11] (a) R.T. Boere, V. Klassen, G. Wolmershauser, J. Chem. Soc. Dalton Trans. (1998) 4147–4154;
(b) A. Kraft, J. Chem. Soc. Perkin Trans. I (1999) 705–714;
(c) K. Sasaki, Y.-X. Zhang, K. Okuda, T. Hirota, J. Heterocycl. Chem. 38 (2001) 425–429.
[12] R.J. Koshar, C.D. Wright, J. La M. Zollinger, D.H. Dybvig, D.R. Husted, US 3726903 (1973).
[13] (a) G. Resnati, V.A. Soloshonok, Tetrahedron Symposia-in Print no. 58, Tetrahedron 52 (1996) 1, 319–330.
(b) R.E. Banks, J.C. Tatlow, B.E. Smart, Organofluorine Chemistry: Principles and Commercial Applications, Plenum Press, New York, 1994
(c) G.K.S.A.K. Prakash, Yudin, Chem. Rev. 97 (1997) 757–786.
[14] (a) T. Kitazume, J.T. Lin, T. Yamamoto, T. Yamazaki, J. Am. Chem. Soc. 113 (1991) 8573–8575;
(b) J.T. Welch, Selective Fluorination in Organic and Bioorganic Chemistry, ACS Symposium Series, vol. 456, American Chemical Society, Whashington, DC, 1991;
(c) R. Filler, Y. Kobayashi, L.M. Yagupolskii, Biomedical Aspects of Fluorine Chemistry, Elsevier, Amsterdam, 1993;
(d) J.T. Welch, S. Eswarakrishnan, Fluorine in Bioorganic Chemistry, Wiley, Chichester, 1991.
[15] (a) Y.M. Wu, Y. Li, J. Deng, J. Fluorine Chem. 126 (2005) 791–795;
(b) Y.M. Wu, Y. Li, J. Deng, Tetrahedron Lett. 46 (2005) 5357–5360;
(c) Y.M. Wu, Y. Li, J. Fluorine Chem. 127 (2006) 223–228;
(d) Y.M. Wu, M. Zhang, Y.Q. Li, J. Fluorine Chem. 127 (2006) 218–222.
[16] G. Hafelinger, F.K.H. Kuske, General and theoretical aspects of amides and related compounds, in: S. Patai, Z. Rappoport (Eds.), The Chemistry of Amidines and Imidates, vol. 2, John Wiley & Sons, New York, 1991, p. 1.
[17] (a) I. Ashworth, P. Hopes, D. Levin, I. Patel, R. Salloo, Tetrahedron Lett. 43 (28) (2002) 4931–4933;
(b) U. Rose, M. Drager, J. Med. Chem. 35 (1992) 2238–2243.
[18] The crystal data of **5ce** has been deposited at the Cambridge Crystallographic Data Center and allocated the deposition number is CCDC 294496. Crystal system, space group: monoclinic, $P2(1)/n$. Unit cell dimensions: $a = 10.1228(11)$ Å, $b = 7.5111(8)$ Å, $c = 24.575(3)$ Å, $\alpha = 90^\circ$, $\beta = 97.089(3)^\circ$, $\gamma = 90(3)^\circ$; volume: 1854.2(4) Å^3; Z, calculated density: 4, 1.303 mg/m^3; absorption coefficient: 0.229 mm^{-1}; $F(0\,0\,0)$: 708; crystal size: 0.240 mm × 0.105 mm × 0.076 mm; theta range for data collection: 1.67–25.50°; completeness to theta = 25.50, 99.5%; data/restraints/parameters: 3428/2/242; goodness-of-fit on F^2: 1.081; final R indices [$I > 2\sigma(1)$]: $R1 = 0.0902$, $wR2 = 0.2056$; R indices (all data): $R1 = 0.1376$, $wR2 = 0.2331$; largest diff. peak and hole: 0.342 and −0.317 Einstein Å^{-3}.