Journal of Fluorine Chemistry 146 (2013) 70–75

Contents lists available at SciVerse ScienceDirect

Journal of Fluorine Chemistry

journal homepage: www.elsevier.com/locate/fluor

Microwave-assisted amination from fluorobenzenes without catalyst and strong base

Xiangguo Meng, Zhengyan Cai, Sa Xiao, Weicheng Zhou *

State Key Lab of New Drug & Pharmaceutical Process, Shanghai Key Lab of Anti-infectives, Shanghai Institute of Pharmaceutical Industry, State Institute of Pharmaceutical Industry, 1111 North Zhongshan No. 1 Rd, Shanghai 200437, PR China

ARTICLE INFO

Article history:
Received 19 September 2012
Received in revised form 15 November 2012
Accepted 4 December 2012
Available online 12 December 2012

Keywords:
Microwave-assisted
Amination
Fluorobenzenes
Nucleophilic substitution
Regioselectivity

ABSTRACT

A facile and versatile amination of fluorobenzenes has been developed in good to excellent yields under microwave irradiation in N-methylpyrrolidinone (NMP) without strong base and catalyst. The presence of additional halogen atom(s) enhanced the leaving ability of fluorine and *meta* fluorine gave higher activation than the *ortho*. It is remarkable that 1,2,3-trifluorobenzene, 1,2,4-trifluorobenzene and 1,2,4,5-tetrafluorobenzene can produce the regioselective mono-substituted products.

1. Introduction

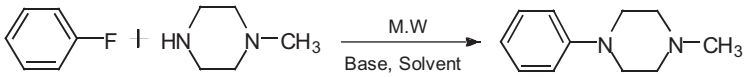
Fluorine substituted anilines represent an important N-aryl motif, which have various potential applications in many areas such as chemistry [1], natural products [2], agrochemical industry [3], fluorescence probes [4], pharmaceutical [5], photography system [6] and materials [7]. Traditional aromatic nucleophilic substitutions (S_NAr), which are limited to only activated aromatic substrates having electron-withdrawing group such as nitro or cyano group, generally afford only moderate yields under harsh conditions to prepare aniline derivatives [8]. Metal-catalyzed coupling reactions (Buchwald-Hartwig reaction) have received enormous interest over the past few decades, with great strides achieved in amination of aryl halides [9–13], triflates [14,15] and carboxylates [16] as effective electrophiles. Disadvantages are the high price of metal catalysts, and the need for kinds of relatively costly ligands. The synthesis of aniline derivatives by the classical Cu-mediated Ullmann condensation, which needs substantial amounts of copper and high temperature, has been known since the beginning of the 20th century. Although Ullmann reactions [17–20] have been extensively developed in aryl C–N bond formation, the cost and availability of the catalysts are still major factors of hindering application [21]. At the same time, long reaction time, sensitive conditions, and/or strong bases are required. In addition, the use of transition metals introduces a challenge for removal of trace amount of the heavy metal in the pharmaceutical product. New strategy, following the standard of green chemistry, for the preparation of fluorine substituted aniline is needed.

Microwave irradiation has been an available method in organic synthesis, which has been applied in heterocycle chemistry, cycloaddition and catalysis reaction [22–25] etc., since the first report of a microwave synthesis in the year 1986 up to now [26]. Microwave irradiation has certain benefits over conventional heating such as acceleration of reaction rate, milder reaction conditions, higher yield, lower energy consumption, enhancement of the selectivity of reaction and easier workup. More recently, it has been reported that ArX (X = Cl, Br or I) could couple with amines to give corresponding anilines using microwave in the presence of a hygroscopic, strong base (KO^tBu) [27]. Aryl triflates, which need to be prepared from phenols, were used to react with amines to obtain anilines derivatives under microwave irradiation [28]. To the best of our knowledge, however, the direct amination of fluorobenzenes employing microwave techniques without strong base has not been described. Herein we wish to report our preliminary research on the microwave-assisted nucleophilic substitution of fluorobenzenes with 1-methylpiperazine, morpholine and piperazine. Without any strong base or catalyst, the reaction smoothly carried out in relatively short time to give the desired products in good yields.

* Corresponding author. Fax: +86 21 3505 2484.
E-mail address: profzhouwc@yahoo.com.cn (W. Zhou).

0022-1139/$ – see front matter © 2012 Elsevier B.V. All rights reserved.
http://dx.doi.org/10.1016/j.jfluchem.2012.12.001

Table 1
Optimization investigation.[a]



Entry	Solvent	Base	Temp (°C)	Catalyst	Time (h)	Yield (%)[b]
1	Fluorobenzene	K_2CO_3	110	–	0.25	0
2	Fluorobenzene	K_2CO_3	210	–	1	0
3[c]	Fluorobenzene	KOH	110	–	0.25	0
4[c]	Fluorobenzene	KO^{t}Bu	110	–	0.25	0
5	EtOH	K_2CO_3	170	–	1	little
6	H_2O	K_2CO_3	160	–	1	little
7	H_2O	K_2CO_3	160	TBAB	1	little
8	DMSO	K_2CO_3	200	–	3	14
9	NMP	K_2CO_3	235	–	2	14
10	NMP	K_2CO_3	250	–	6	28
11	NMP	K_2CO_3	250	–	20	67

[a] Reaction conditions: 1-fluorobenzene (30 mmol), base (20 mmol), 1-methylpiperazine (10 mmol), 15 mL solvent, and/or 5 mol% TBAB were charged to a 20 mL sealed microwave vial equipped with a magnetic stir bar, which can bear the maximum operating pressure of 20 bar, at the temperature indicated for 0.25–20 h.
[b] Isolated yields.
[c] The suspension of KOH or KO^{t}Bu in fluorobenzene was so bad that the reactor automatically ceased the heating.

2. Results and discussion

At first, 1-fluorobenzene, which would have the lowest reactivity among fluorobenzenes was chosen as our initial substrate in the reaction with 1-methylpiperazine. The research protocol included screening for solvent, base, temperature, reaction time and catalyst. Our preliminary experiments demonstrated that no product was found when excess of 1-fluorobenzene was served as solvent in the presence of K_2CO_3, KOH, or KO^{t}Bu (Table 1, entries 1–4). Some polar protic solvents (EtOH or H_2O) with phase-transfer catalyst tetrabutylammonium bromide (TBAB) were tested, but these conditions did not improve the reaction (Table 1, entries 5–7). High boiling point solvent, such as DMSO and N-methylpyrrolidinone (NMP), were proved to be more effective for the microwave-assisted amination. DMSO as the solvent in the presence of K_2CO_3 delivered the expected 1-methyl-4-phenylpiperazine (Table 1, entry 8), and NMP gave the better result, especially when the reaction was carried for long time (Table 1, entries 9–11).

With the optimized conditions, we evaluated the microwave-assisted amination of a series of fluorobenzenes (1,2-difluorobenzene, 1-cholor-2-fluorobenzene, 1,2,3-trifluorobenzene, 1,2,4-trifluorobenzene and 1,2,4,5- tetrafluorobenzene) with 1-methylpiperazine, morpholine and piperazine (Table 2). The yield of

Table 2
Amination of various fluorobenzenes and amines under microwave irradiation.[a]

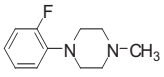
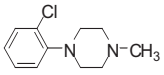
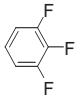
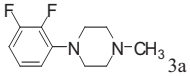
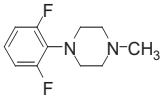
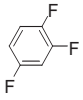
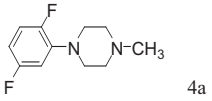
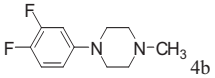
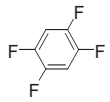
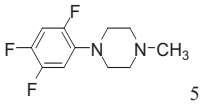
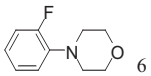
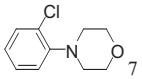
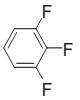
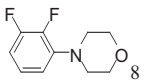
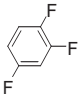
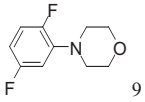
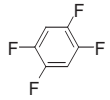
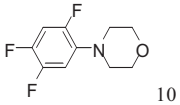
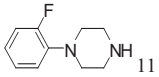
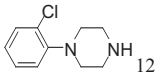
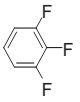
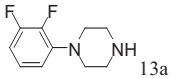
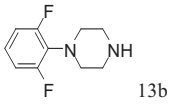
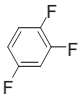
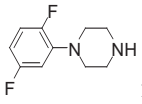
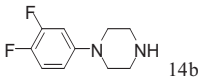
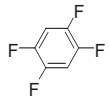
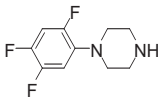
Entry	Fluorobenzenes	Amines	Temp (°C)	Time (h)	Product	Yield (%)[b]
1		1-Methylpiperazine	250	1	 1	27[c]
				3		38[c]
				6		85[c]
2		1-Methylpiperazine	250	6	 2	81[c]
3		1-Methylpiperazine	220	1.5	 3a	81[c]
					 3b	
					3a:3b = 19:1	
4		1-Methylpiperazine	220	3	 4a	84[c,e]
					 4b	

Table 2 (*Continued*)

Entry	Fluorobenzenes	Amines	Temp (°C)	Time (h)	Product	Yield (%)[b]
					4a:4b = 17:1	
5		1-Methylpiperazine	220	1	 5	90[c]
6		Morpholine	250	6	 6	60[c]
7		Morpholine	250	6	 7	55[c]
8		Morpholine	190	2.5	 8	72[c]
9		Morpholine	200	2	 9	68[c]
10		Morpholine	220	1.5	 10	86[c]
11		Piperazine	250	2	 11	70[d]
12		Piperazine	250	3	 12	61[d]
13		Piperazine	190	1	 13a  13b	73[d,e]
					13a:13b = 21:1	
14		Piperazine	220	2	 14a  14b	92[d,e]
					14a:14b = 19:1	
15		Piperazine	190	1	 15	87[d]

[a] All reactions were carried out under sealed-tube conditions in a Biotage Initiator microwave reactor with the following settings: prestir = 20 s; absorption level: very high; fixed hold time: on. For a detailed experimental operation, see Section 4

[b] Yields of isolated products.

[c] Yield was based on amines (fluorobenzene: amine = 3:1).

[d] Yield was based on fluorobenzenes (fluorobenzene: amine = 1:3).

[e] The ratios were determined by HPLC analysis, which was performed using a Waters 1525Pump, 2998PAD, 2707Autosampler, SunFire C18 4.6 mm × 150 mm, 5 μm column with a 30 min linear gradient from 5:95 to 30:70 CH_3CN:0.1%TFA at a flow rate of 2 mL/min, with UV dectection at 236 nm.

amination product increased along with the extension of the reaction time in the case of 1,2-difluorobenzene (Table 2, entry 1). The reactivity of fluorobenzenes was enhanced along with the increase in the fluorine atoms on the benzene ring (Table 2, entries 6–10). Fluorine atom had a better activation than chlorine (Table 2, entries 1 and 2, entries 6 and 7, entries 11 and 12). Isomers of trifluorobenzene (Table 2, entries 3 and 4, entries 13 and 14) put forward the question of regioselectivity. Because of the weaker nucleophilicity of morpholine, among the possible products, only 8 or 9 potential products was produced from corresponding trifluorobenzene (Table 2, entries 8 and 9). In entry 8, flanking fluorine atom was activated by both of the other fluorines (*ortho* and *meta*) and the central fluorine was activated by two *ortho* fluorines. Since the presence of a fluorine atom at the *meta* position to the fluorine as leaving group enhanced its reactivity compared to *ortho* position [29,30], compound 8 was obtained as the sole amination product. Meanwhile, a similar situation happened to entry 9. While the nucleophilicity both of 1-methylpiperazine and piperazine were better than morpholine [31], little byproduct were detected by HPLC analysis (Table 2, entries 3 and 4, entries 13 and 14). **3b** and **13b** were prepared by reversed-phase preparative HPLC (5–9% CH_3CN in water containing 0.1%TFA, C18 19 mm × 100 mm, 5 μm SunFire™ prep OBD™). It was noteworthy that 1,2,4,5-tetrafluorobenzene was the most reactive substrate in this paper, giving the best yields in the shortest time (Table 2, entries 5, 10 and 15). The ratio of fluorobenzenes/amines was changed from 3:1 to 1:3 in order to avoid the bis-phenyl piperazine (Table 2, entries 11–15). In these cases, no multi-piperazinyl benzene products were found since other fluorines were inactivated by piperazinyl group. Additionally, we investigated the possibility for this amination using traditional heating methods and found that 1-fluorobenzene did not react with 1-methylpiperazine in NMP at 90 °C for 5 days. Meanwhile under the similar condition, 1,2,4,5-tetrafluorobenzene gave the corresponding aniline only in 10% yield.

The ^1H NMR data (400 MHz) were very helpful to identify **3a** and **3b**. For **3a**, the multiple-peak at 7.13 ppm was assigned to the hydrogen at the *meta* position to methylpiperazinyl and the coupling constants of $J_{H-H(o)}$, $J_{H-F(m)}$, $J_{H-F(p)}$ were calculated as 8.4 Hz, 6.1 Hz and 2.0 Hz, respectively, another peak at 7.04 ppm was assigned to the hydrogen at the *para* position to methylpiperazinyl with the coupling constants of $J_{H-F(o)}$ = 10.0 Hz, $J_{H-H(o)}$ = 8.4 Hz, $J_{H-F(m)}$ = 6.9 Hz and $J_{H-H(m)}$ = 1.6 Hz. The triple peak at 6.93 ppm could be assigned to the hydrogen at the *ortho* position to methylpiperazinyl. For **3b**, only two groups of multiple-peak, which were assigned to the aromatic protons, were observed at 6.92 ppm (2H) and 6.84 ppm (1H). The similar spectral profile was found for **13a** and **13b** (see Section 4).

3. Conclusion

We have established a facile and versatile method for the preparation of halogenated anilines from halogenated fluorobenzenes in good or excellent yield under microwave-assisted reaction without strong base and catalyst. The presence of additional halogen atom(s) enhanced the leaving ability of fluorine and *meta* fluorine gave higher activation than the *ortho*, so that the regioselectivity was achieved. It was noteworthy that 1,2,3-trifluorobenzene, 1,2,4-trifluorobenzene and 1,2,4,5-tetrafluorobenzene only produced the mono-substituted products.

4. Experimental

4.1. General information

The materials and reagents were used as purchased and NMP was used without any additional purification. Analytical thin-layer chromatography (TLC) was performed on gel F_{254} plates. The silica gel (300–400 meshes) for column chromatography was purchased from the Qingdao Marine Chemical Factory in China. The NMR spectra were recorded on Varian INOVA-400 (400 MHz) or Bruker AV400 (400 MHz) spectrometer. ^1H spectra were run at 400 MHz and ^{13}C spectra were run at 100 MHz in $CDCl_3$ or DMSO-d_6. Chemical shifts were related to that of the solvent. ^{19}F NMR spectra were obtained using $CFCl_3$ as an internal standard. HR-MS were recorded on an Agilent G-1969A spectrometer. The melting points were determined by capillary method. Microwave reaction was performed on Biotage microwave reactor (Initiator Exp EU355301, 108115-45U).

4.2. General procedure

Fluorobenzenes (3eq, 30 mmol), amines (1 eq, 10 mmol), K_2CO_3 (2 eq) and NMP (15 mL) were charged to a 20 mL microwave vial equipped with a magnetic stir bar. The vial was capped and heated in the Biotage Initiator microwave reactor (with following setting: prestir = 20 s; absorption level = very high; fixed hold time = on) for 1–6 h at 190–250 °C as indicated. After cooling to 50 °C, the vial was opened and the contents were transferred to a separatory funnel containing water (60 mL) and extracted with ethyl acetate (15 mL × 4). The combined organic extracts were washed with water, and dried over anhydrous Na_2SO_4. After removal of the solvent, the residues were purified by the column chromatography on silica gel to give the pure product.

4.2.1. 1-Methyl-4-phenylpiperazine

^1H NMR(400 MHz, DMSO-d_6): δ 7.26–7.22 (t, 2H, *J* = 7.2 Hz, Ph), 6.98–6.96 (d,

2H, *J* = 7.6 Hz, Ph), 6.88–6.85 (t, 1H, *J* = 7.2 Hz, Ph), 3.73–3.46 (m, 4H, piperazine), 3.13–3.00 (m, 4H, piperazine), 2.81 (s, 3H, $-CH_3$)

4.2.2. 1-(2-Fluorophenyl)-4-methylpiperazine (**1**)

A colorless oil.

^1H NMR(400 MHz, $CDCl_3$): δ 7.28–6.95 (m, 4H, Ph), 3.17–3.14 (t, 4H, *J* = 4.8 Hz, piperazine), 2.64–2.62 (t, 4H, *J* = 4.8 Hz, piperazine), 2.38 (s, 3H, $-CH_3$)

4.2.3. 1-(2-Chlorophenyl)-4-methylpiperazine (**2**)

A colorless oil.

^1H NMR(400 MHz, $CDCl_3$): δ 7.38–7.36 (d, 1H, *J* = 7.2 Hz, Ph), 7.23–7.21 (t, 1H, *J* = 7.2 Hz, 8.0 Hz, Ph), 7.08–7.06 (d, 1H, *J* = 8.0 Hz, Ph), 7.00–6.96 (t, 1H, *J* = 7.2 Hz, Ph), 3.12–3.10 (t, 4H, *J* = 4.0 Hz, piperazine), 2.64–2.62 (t, 4H, *J* = 4.0 Hz, piperazine), 2.38 (s, 3H, $-CH_3$)

4.2.4. 1-(2,4,5-Trifluorophenyl)-4-methylpiperazine (**5**)

A colorless oil.

^1H NMR(400 MHz, $CDCl_3$) δ 7.28–6.86 (octet, 1H, $J_{H-F(o)}$ = 11.6 Hz, 10.4 Hz, $J_{H-F(m)}$ = 7.4 Hz, Ph), 6.80–6.73 (sextet, 1H, $J_{H-F(o)}$ = 12.0 Hz, $J_{H-F(m)}$ = 8.1 Hz, 8.0 Hz, Ph), 3.07–3.05 (t, 4H, *J* = 4.4 Hz, piperazine), 2.60–2.58 (t, 4H, *J* = 4.4 Hz, piperazine), 2.36 (s, 3H, $-CH_3$).

4.2.5. 4-(2-Fluorophenyl)morpholine (**6**)

A white solid, m.p: 39–40 °C.

^1H NMR(400 MHz, $CDCl_3$) δ 7.28–7.02 (m, 2H, Ph), 6.99–6.94 (m, 2H, Ph), 3.90–3.88 (t, 4H, *J* = 4.8 Hz, morpholine), 3.12–3.10 (t, 4H, *J* = 4.8 Hz, morpholine)

4.2.6. 4-(2-Chlorophenyl)morpholine (**7**)

A white solid, m.p: 66–67 °C.

^1H NMR(400 MHz, $CDCl_3$) δ 7.40–7.38 (q, 1H, $J_{H-H(o)}$ = 8.0 Hz, $J_{H-H(m)}$ = 1.4 Hz, Ph), 7.27–7.23 (sextet, 1H, $J_{H-H(o)}$ = 7.8 Hz, 7.6 Hz, $J_{H-H(m)}$ = 1.5 Hz, Ph), 7.07–7.05 (q, 1H, $J_{H-H(o)}$ = 8.0 Hz, J_{H-

$J_{H-H(m)}$ = 1.2 Hz, Ph), 7.03–6.99 (sextet, 1H, $J_{H-H(o)}$ = 7.6 Hz, 7.6 Hz, $J_{H-H(m)}$ = 1.6 Hz, Ph), 3.91–3.89 (t, 4H, J = 4.4 Hz, morpholine), 3.09–3.07 (t, 4H, J = 4.4 Hz, morpholine)

*4.2.7. 4-(2,3-Difluorophenyl)morpholine (**8**)*

A white solid, m.p: 77–78 °C.

^{1}H NMR(400 MHz, $CDCl_3$) δ 7.28–6.96 (m, 1H, $J_{H-H(o)}$ = 8.4 Hz, 8.2 Hz, $J_{H-F(m)}$ = 6.0 Hz, $J_{H-F(p)}$ = 2.3 Hz, Ph), 6.84–6.77 (m, 1H, $J_{H-F(o)}$ = 9.6 Hz, $J_{H-H(o)}$ = 8.4 Hz, $J_{H-F(m)}$ = 7.0 Hz, $J_{H-H(m)}$ = 1.4 Hz, Ph), 6.72–6.67 (m, 1H, $J_{H-H(o)}$ = 8.4 Hz, $J_{H-F(m)}$ = 7.0 Hz, $J_{H-F(p)}$ = 1.4 Hz, $J_{H-H(m)}$ = 1.4 Hz, Ph), 3.89–3.87 (m, 4H, morpholine), 3.13–3.11 (m, 4H, morpholine)

^{13}C NMR(100 MHz, DMSO-d_6) δ 152.44–149.91 (q, 1C, J_{C-F} = 241.8 Hz, $J_{C-F(o)}$ = 11.7 Hz, Ph), 144.60–144.29 (d, 1C, J_{C-F} = 230.3 Hz, Ph), 142.30–141.98 (q, 1C, $J_{C-F(o)}$ = 18.1 Hz, $J_{C-F(m)}$ = 8.9 Hz, Ph), 124.93–124.79 (q, 1C, $J_{C-F(m)}$ = 8.5 Hz, $J_{C-F(p)}$ = 4.7 Hz, Ph), 114.77 (s, 1C, Ph), 110.34–110.17 (d, 1C, $J_{C-F(o)}$ = 17.3 Hz, Ph), 66.53 (s, 2C, morpholine), 50.88–50.85 (d, 2C, morpholine).

^{19}F NMR(376 MHz, DMSO-d_6) δ −139.20 (d, 1F), -149.94 (d, 1F)

HR-MS: for $C_{10}H_{11}F_2NO$ $[M+H]^+$ calculated 200.0887, found 200.0888.

*4.2.8. 4-(2,5-Difluorophenyl)morpholine (**9**)*

A white solid, m.p: 84–85 °C.

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.00–6.94 (m, 1H, $J_{H-F(o)}$ = 12 Hz, $J_{H-H(o)}$ = 8.8 Hz, $J_{H-F(m)}$ = 5.1 Hz, Ph), 6.67–6.58 (m, 2H, Ph), 3.89–3.86 (t, 4H, J = 4.4 Hz, morpholine), 3.11–3.08 (t, 4H, J = 4.4 Hz, morpholine)

^{13}C NMR(100 MHz, $CDCl_3$): δ 160.34–157.94 (q, 1C, J_{C-F} = 239 Hz, $J_{C-F(p)}$ = 2.1 Hz, Ph), 152.86–150.43 (q, 1C, J_{C-F} = 239 Hz, $J_{C-F(p)}$ = 2.7 Hz, Ph), 141.14–140.95 (t, 1C, $J_{C-F(m)}$ = 9.5 Hz, $J_{C-F(o)}$ = 19.1 Hz, Ph), 116.69–116.35 (q, 1C, $J_{C-F(o)}$ = 23.9 Hz, $J_{C-F(m)}$ = 10.1 Hz, Ph), 107.93–107.62 (q, 1C, $J_{C-F(o)}$ = 23.9 Hz, $J_{C-F(m)}$ = 8.0 Hz, Ph), 105.94–105.68 (d, 1C, $J_{C-F(o)}$ = 25.5 Hz, Ph), 66.77 (s, 2C, morpholine), 50.56 (d, 2C, morpholine)

^{19}F NMR(376 MHz, DMSO-d_6) δ −117.00 (d, 1F), −128.11 (d, 1F)

HR-MS: for $C_{10}H_{11}F_2NO$ $[M+H]^+$ calculated 200.0881, found 200.0873.

*4.2.9. 4-(2,4,5-Trifluorophenyl)morpholine (**10**)*

A white solid, m.p: 59–60 °C.

^{1}H NMR(400 MHz, $CDCl_3$) δ 6.96–6.89 (octet, 1H, $J_{H-F(o)}$ = 11.6 Hz, 10.0 Hz, $J_{H-F(m)}$ = 7.6 Hz, Ph), 6.80–6.73 (sextet, 1H, $J_{H-F(o)}$ = 12.0 Hz, $J_{H-F(m)}$ = 8.0 Hz, 8.0 Hz, Ph), 3.88–3.85 (t, 4H, J = 4.8 Hz, morpholine), 3.04–3.02 (t, 4H, J = 4.8 Hz, morpholine)

^{13}C NMR(100 MHz, DMSO-d_6) δ 151.63–149.12 (q, 1C, J_{C-F} = 243.1 Hz, $J_{C-F(m)}$ = 8.1 Hz, Ph), 147.53–145.18 (q, 1C, J_{C-F} = 225.0 Hz, $J_{C-F(m)}$ = 12.6 Hz, Ph), 145.02–142.75 (q, 1C, J_{C-F} = 226.8 Hz, $J_{C-F(o)}$ = 13.5 Hz, Ph), 137.34 (s, 1 C, Ph), 108.38–108.14 (m, 1C, Ph), 107.00–106.51 (m, 1C, Ph), 66.48 (s, 2C, morpholine), 50.95–50.93 (d, 2C, morpholine)

^{19}F NMR(376 MHz, DMSO-d_6) δ −124.19 (d, 1F), −142.08 (q, 1F), −144.61 (d, 1F)

HR-MS: for $C_{10}H_{10}F_3NO$ $[M+H]^+$ calculated 218.0787, found 218.0794.

*4.2.10. 1-(2-Fluorophenyl)piperazine (**11**)*

A colorless oil.

^{1}H NMR(400 MHz, $CDCl_3$ + D_2O) δ 7.29–6.94 (m, 4H, Ph), 3.09–3.07 (m, 8H, piperazine)

*4.2.11. 1-(2-Chlorophenyl)piperazine (**12**)*

A colorless oil.

^{1}H NMR(400 MHz, $CDCl_3$ + D_2O) δ 7.39–7.36 (q, 1H, $J_{H-H(o)}$ = 7.6 Hz, $J_{H-H(m)}$ = 1.4 Hz, Ph), 7.26–7.22 (sextet, 1H, $J_{H-H(o)}$ = 7.6 Hz, 7.6 Hz, $J_{H-H(o)}$ = 1.6 Hz, Ph), 7.07–7.05 (q, 1H, $J_{H-H(o)}$ = 7.6 Hz, $J_{H-H(m)}$ = 1.8 Hz, Ph), 7.00–6.96 (sextet, 1H, $J_{H-H(o)}$ = 7.6 Hz, 7.6 Hz, $J_{H-H(m)}$ = 1.6 Hz, Ph), 3.08–3.03 (m, 8H, piperazine)

*4.2.12. 1-(2,4,5-Trifluorophenyl)piperazine (**15**)*

A colorless oil.

^{1}H NMR(400 MHz, $CDCl_3$ + D_2O) δ 7.26–6.82 (octet, 1H, $J_{H-F(o)}$ = 11.2 Hz, 10.2 Hz, $J_{H-F(m)}$ = 7.5 Hz, Ph), 6.76–6.69 (sextet, 1H, $J_{H-F(o)}$ = 12.0, $J_{H-F(m)}$ = 8.0 Hz, 8.0 Hz, Ph), 3.01–2.94 (m, 8H, piperazine)

4.3. Purification of 3a, 4a, 13a and 14a

The major product (as colorless oil) of entry 3 after column chromatography was **3a** which was contaminated with **3b**. The component was separated by salt formation in HCl/MeOH, and the major product (**3a**) was purified by crystallization from ethyl acetate/ethanol. The mother solution was served for preparing **3b** by preparative HPLC. Compounds **4a**, **13a** and **14a** were purified in the similar manner.

*4.3.1.1. 1-(2,3-Difluorophenyl)-4-methylpiperazine hydrochloride (**3a** HCl)*

A solid, m.p: 220–222 °C.

^{1}H NMR(400 MHz, DMSO-d_6) δ 7.16–7.10 (m, 1H, $J_{H-H(o)}$ = 8.4 Hz, $J_{H-F(m)}$ = 6.1 Hz, $J_{H-F(p)}$ = 2.0 Hz, Ph), 7.07–7.00 (m, 1H, $J_{H-F(o)}$ = 10.0 Hz, $J_{H-H(o)}$ = 8.4 Hz, $J_{H-F(m)}$ = 6.9 Hz, $J_{H-H(m)}$ = 1.6 Hz, Ph), 6.95–6.91 (m, 1H, $J_{H-H(o)}$ = 7.8 Hz, $J_{H-F(m)}$ = 6.4 Hz, $J_{H-H(m)}$ = 1.2 Hz, Ph), 3.30 (brs, 8H, piperazine), 2.79 (s,3H, $-CH_3$)

*4.3.1.2. 1-(2,5-Difluorophenyl)-4-methylpiperazine (**4a**)*

A colorless oil.

^{1}H NMR(400 MHz, $CDCl_3$) δ 6.96–6.89 (m, 1H, $J_{H-F(o)}$ = 12.0 Hz, $J_{H-H(o)}$ = 8.8 Hz, $J_{H-F(m)}$ = 5.2 Hz, Ph), 6.65–6.60 (m, 1H, $J_{H-F(o)}$ = 13.2 Hz, $J_{H-F(m)}$ = 6.6 Hz, $J_{H-H(m)}$ = 3.3 Hz, Ph), 6.59–6.54 (m, 1H, Ph), 3.13–3.10 (t, 4H, J = 4.8 Hz, piperazine), 2.59–2.57 (t, 4H, J = 4.8 Hz, piperazine), 2.35 (s, 3H, $-CH_3$)

^{13}C NMR(100 MHz, DMSO-d_6) δ 160.17–157.79 (d, 1 C, J_{C-F} = 238.7 Hz, Ph), 152.54–150.16 (d, 1C, J_{C-F} = 238.6 Hz, Ph), 140.00–139.81 (t, 1C, $J_{C-F(o)}$ = 19.8 Hz, $J_{C-F(m)}$ = 9.9 Hz, Ph), 117.65–117.31 (q, 1C, $J_{C-F(o)}$ = 23.4 Hz, $J_{C-F(m)}$ = 10.0 Hz, Ph), 109.19–108.87 (q, 1C, $J_{C-F(o)}$ = 23.9 Hz, $J_{C-F(m)}$ = 8.3 Hz, Ph), 107.43–107.17 (d, 1C, $J_{C-F(o)}$ = 26.3 Hz, Ph), 52.48 (s, 2C, piperazine), 47.12–47.09 (*d*, 2C, piperazine), 42.42 (s, 1C, $-CH_3$)

^{19}F NMR(376 MHz, DMSO-d_6) δ −116.74 (d, 1F), 127.94 (d, 1F)

HR-MS: for $C_{11}H_{14}F_2N_2$ $[M+H]^+$ calculated 213.1198, found 213.1202.

*4.3.1.3. 1-(2,3-Difluorophenyl)piperazine (**13a**)*

A colorless oil.

^{1}H NMR(400 MHz, $CDCl_3$ + D_2O) δ 7.01–6.94 (m, 1H, $J_{H-H(o)}$ = 8.0 Hz, 8.0 Hz, $J_{H-F(m)}$ = 5.7 Hz, $J_{H-F(p)}$ = 2.2 Hz, Ph), 6.82–6.75 (m, 1H, $J_{H-F(o)}$ = 9.6 Hz, $J_{H-H(o)}$ = 8.0 Hz, $J_{H-F(m)}$ = 6.8 Hz, $J_{H-H(m)}$ = 1.2 Hz, Ph), 6.73–6.69 (m, 1H, $J_{H-H(o)}$ = 7.8 Hz, $J_{H-F(m)}$ = 6.2 Hz, Ph), 3.10–3.06 (m, 8H, piperazine)

*4.3.1.4. 1-(2,5-Difluorophenyl)piperazine (**14a**)*

A colorless oil.

^{1}H NMR(400 MHz, $CDCl_3$ + D_2O) δ 6.94–6.90 (m, 1H, Ph), 6.64–6.59 (m, 1H, Ph), 6.58–6.55 (m, 1H, Ph), 3.02–3.00 (m, 8H, piperazine)

4.4. Purification of 3b and 13b by preparative HPLC

3b (or **13b**) in the mixture of **3a** (or **13a**) and **3b** (or **13b**) was prepared by reversed-phase preparative HPLC. Preparative HPLC

was performed using SunFire™ prep OBD™ C18 19 × 100 mm, 5 μm column with a 10 min linear gradient from 5:95 to 9:91 CH_3CN:0.1%TFA at a flow rate of 22 mL/min, with UV detection at 236 nm and 280 nm. Solvents and reagents were used as purchased.

*4.4.1. 1-(2,6-Difluorophenyl)-4-methylpiperazine (**3b**)*

A colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ 6.93–6.91 (m, 2H, Ph), 6.86–6.82 (m, 1H, Ph), 3.27–3.25 (t, 4H, J = 4.4 Hz, piperazine), 2.58–2.56 (t, 4H, J = 4.8 Hz, piperazine), 2.37 (s, 3H, $-CH_3$)

^{13}C NMR (100 MHz, DMSO-d_6) δ 159.63–157.11 (q, 2 C, J_{C-F} = 245.0 Hz, $J_{C-F(m)}$ = 6.9 Hz, Ph), 126.91–126.65 (t, 1 C, $J_{C-F(o)}$ = 26.5 Hz, Ph), 125.69–125.48 (t, 2C, $J_{C-F(o)}$ = 20.5 Hz, Ph), 113.16–112.91 (q, 1C, $J_{C-F(m)}$ = 6.3 Hz, Ph), 53.48 (s, 2C, piperazine), 48.11 (s, 2C, piperazine), 42.68 (s, 1C, $-CH_3$)

^{19}F NMR (376 MHz, DMSO-d_6) δ −120.17 (s, 2F)

HR-MS: for $C_{11}H_{14}F_2N_2$ $[M+H]^+$ calculated 213.1198, found 213.1204.

*4.4.2. 1-(2,6-Difluorophenyl)piperazine (**13b**)*

A colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) δ 6.97–6.90 (m, 2H, Ph), 6.86–6.81 (m, 1H, Ph), 3.19–3.16 (t, 4H, J = 4.8 Hz, piperazine), 3.00–2.98 (t, 4H, J = 4.8 Hz, piperazine)

Acknowledgements

This work was supported by 973 program of the Ministry of Science and Technology of China (2010CB735601 and 2012CB724501).

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jfluchem.2012.12.001.

References

[1] S. Suwanprasop, T. Nhujak, S. Roengsumran, A. Petsom, Ind. Eng. Chem. Res. 43 (2004) 4973–4978.
[2] F. He, B.M. Foxman, B.B. Snider, J. Am. Chem. Soc. 120 (1998) 6417–6418.
[3] K. Weissermel, H.J. Arpe, Industrial Organic Chemistry, Wiley-VCH, Weinheim, Germany, 2007.
[4] S.R. Stauffer, J.F. Hartwig, J. Am. Chem. Soc. 125 (2003) 6977–6985.
[5] Y.P. Hong, G.J. Tanoury, H.S. Wilkinson, R.P. Bakale, S.A. Wald, C.H. Senanayake, Tetrahedron Lett. 38 (1997) 5663–5666.
[6] R.O. Loutfy, C.K. Hsiao, P.M. Kazmaier, Photogr. Sci. Eng. 27 (1983) 5–10.
[7] S.A. Lawrence, Amines: Synthesis, Properties and Application, Cambridge University Press, Cambridge, 2004.
[8] M.B.J. Smith, March in Advanced Organic Chemistry Reactions Mechanisms and Structure, fifth ed., John Wiley & Sons, New York, 2001 (Chaper 13), pp. 850–893.
[9] M. Kim, S. Chang, Org. Lett. 12 (2010) 1640–1643.
[10] T. Tu, W.-W. Fang, J. Jiang, Chem. Commun. 47 (2011) 12358–12360.
[11] F.-F. Yong, Y.-C. Teo, Tetrahedron Lett. 51 (2010) 3910–3912.
[12] S. Lavy, J.J. Miller, M. Pazicky, A.-S. Rodrigues, F. Rominger, C. Jakel, D. Serra, N. Vinokurov, M. Limbach, Adv. Synth. Catal. 352 (2010) 2993–3000.
[13] R.J. Lundgren, A. Sappong-Kumankumah, M. Stradiotto, Chem. Eur. J. 16 (2010) 1983–1991.
[14] L. Ackermann, R. Sandmann, W.-F. Song, Org. Lett. 13 (2011) 1784–1786.
[15] S.D. Ramgren, A.L. Silberstein, Y. Yang, N.K. Garg, Angew. Chem. Int. Ed. 50 (2011) 2171–2173.
[16] T. Shimasaki, M. Tobisu, N. Chatani, Angew. Chem. Int. Ed. 40 (2010) 2020–2032.
[17] Y. Zhang, S. Patel, N. Mainolfi, T.F. Jamison, Org. Lett. 13 (2011) 280–283.
[18] K. Yang, Y.T. Qiu, S. Jiang, Z.Y. Wang, Z. Li, J. Org. Chem. 76 (2011) 3151–3159.
[19] X.-F. Xia, X.-Z. Shu, K.-G. Ji, Y.-F. Yang, A. Shaukat, X.-Y. Liu, Y.-M. Liang, J. Org. Chem. 6 (2010) 2893–2902.
[20] D.P. Wang, K. Ding, Chem. Commun. 14 (2009) 1891–1893.
[21] Z.J. Zhang, J.C. Mao, D. Zhu, F. Wu, H.L. Chen, B.S. Wan, Catal. Commun. 6 (2005) 784–787.
[22] L. Andre, Microwaves in Organic Synthesis, Wiley-VCH, Weinheim, 2006.
[23] A.J.A. Watson, A.C. Maxwell, J.M.J. Williams, J. Org. Chem. 76 (2011) 2328–2331.
[24] D. Cantillo, B. Gutmann, C.O. Kappe, J. Am. Chem. Soc. 133 (2011) 4465–4475.
[25] G.K. Surya Prakash, H.S. Krishnan, P.V. Jog, A.P. lye, G.A. Olah, Org. Lett. 14 (2012) 1146–1149.
[26] R. Gedye, F. Smith, K. Westaway, H. Ali, L. Baldisera, L. Laberge, J. Rousell, Tetrahedron Lett. 27 (1986) 279–283.
[27] L. Shi, M. Wang, C.-A. Fan, F.-M. Zhang, Y.-Q. Tu, Org. Lett. 5 (2003) 3515–3517.
[28] G. Xu, Y.-G. Wang, Org. Lett. 6 (2004) 985–987.
[29] B. Barlaam, C.S. Harris, J. Lecoq, H.T.H. Nguyen, Tetrahedron 68 (2012) 534–543.
[30] B.A. Kowalczyk, Synthesis 29 (1997) 1411–1414.
[31] Y.C.F. Brotzel, H.M. Chu, J. Org. Chem. 72 (2007) 3679–3688.