A Practical Synthesis of 2-{4-[4-Fluoro-3-(trifluoromethyl)phenyl]-2-(piperidin-4-yl)-1*H*-imidazol-1-yl}-*N*,*N*-dimethylethanamine

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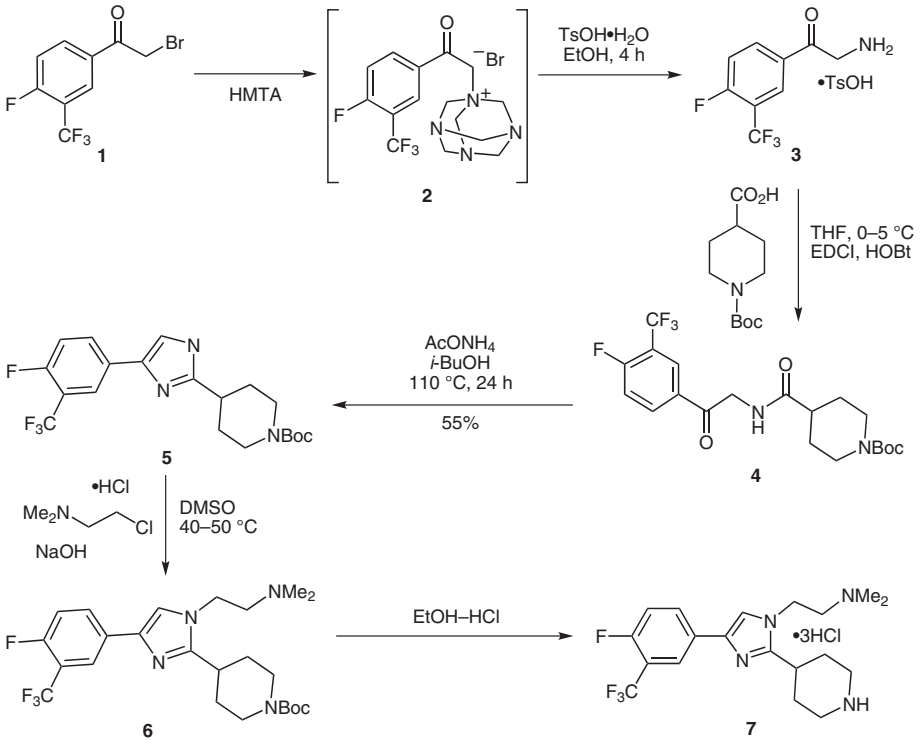
Received: 16.03.2012; Accepted after revision: 26.04.2012

Abstract: A practical synthesis of the title compound was accomplished by hydrogenation of 2-{4-[4-fluoro-3-(trifluoromethyl)phenyl]-2-(pyridin-4-yl)-1*H*-imidazol-1-yl}-*N*,*N*-dimethylethanamine. The latter was obtained by N-alkylation of 4-{4-[4-fluoro-3-(trifluoromethyl)phenyl]-1*H*-imidazol-2-yl}pyridine. Treatment of *N*-{2-[4-fluoro-3-(trifluoromethyl)phenyl]-2-oxoethyl}isonicotinamide hydrochloride with ammonium acetate in acetic acid provided 4-{4-[4-fluoro-3-(trifluoromethyl)phenyl]-1*H*-imidazol-2-yl}pyridine. Coupling of 2-amino-1-[4-fluoro-3-(trifluoromethyl)phenyl]ethanone 4-methylbenzene sulfonate with pyridine 4-carboxylic acid using either T_3P or EDCI-HOBt provided *N*-{2-[4-fluoro-3-(trifluoromethyl)phenyl]-2-oxoethyl}isonicotinamide hydrochloride.

Key words: imidazole, EDCI, T_3P, ammonium acetate, hydrogenation

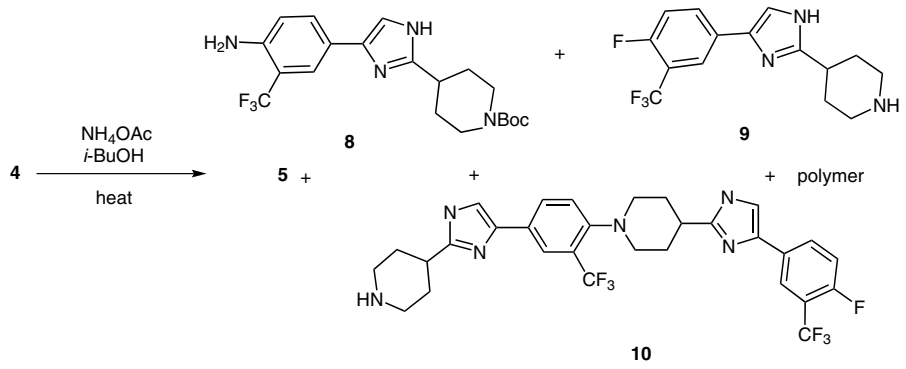
Substituted imidazoles are important heteroaromatic compounds, which not only exhibit a broad range of biological activities such as antifungal properties,[1–10] analgesic activity,[2,3] anti-inflammatory activity inhibiting the p38 MAP kinase or cytokine release,[4,5] and antiallergic activity,[6] but also are important building blocks found in naturally occurring compounds.[7–10] Therefore, we were interested in a robust synthesis of 2-{4-[4-fluoro-3-(trifluoromethyl)phenyl]-2-(piperidin-4-yl)-1*H*-imidazol-1-yl}-*N*,*N*-dimethylethanamine. A survey of literature revealed that synthesis of the title compound can be accomplished in six steps from 2-bromo-1-[4-fluoro-3-(trifluoromethyl)phenyl]ethanone (**1**) (Scheme 1).[11]

The existing synthetic approach to **5**, while well documented, resulted in poor isolated yield of **5** because of oligomerization of the starting material **4** under reaction



Scheme 1 Literature synthesis of compound **7**

SYNTHESIS 2012, 44, 2231–2236
Advanced online publication: 13.06.2012
DOI: 10.1055/s-0031-1290371; Art ID: SS-2012-M0276-OP



Scheme 2 Impurities formed during scale-up of **5**

conditions due to its condensation with **9** derived by the thermal deprotection of Boc group. Thus, in addition to the formation of desired **5**, deprotected product **9**, and significant quantities of aniline analogue **8** along with dimer **10** were observed (Scheme 2). These additional impurities generated in this process along with the specific need for protected imidazole **5** posed challenges during scale-up with respect to reproducibility and purification. Further, N-alkylation of **5** in DMSO at 100 kg scale also resulted in the formation of undesired impurities at significantly high level (8–12%, Figure 1), which made the purification of **6** very difficult resulting in a poor isolated yield.

In order to avoid the above mentioned issues, we were interested in developing a robust synthesis of title compound **18** from **3**. Herein, we report a practical synthesis of title compound as shown in Scheme 3.

Thus, synthesis of **3** was accomplished following the literature procedure.[11] Coupling of acid chloride of **13** with **3** resulted in poor conversion. However, synthesis of **14** was successfully achieved in good yield and purity via activation of acid **13** either by using T_3P (2,4,6-tripropyl-1,2,3,2,4,6-trioxatriphosphorinane-2,4,6-trioxide) or EDCI-HOBt (Table 1).

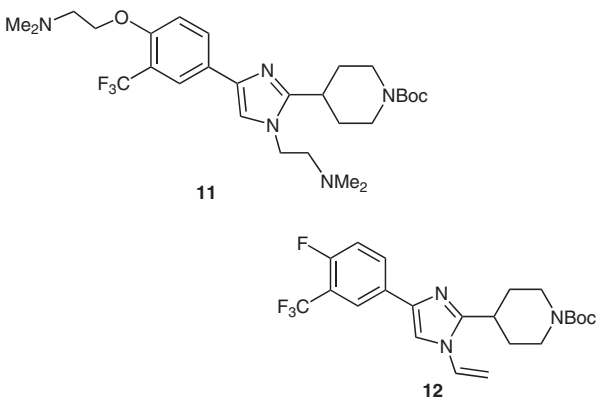
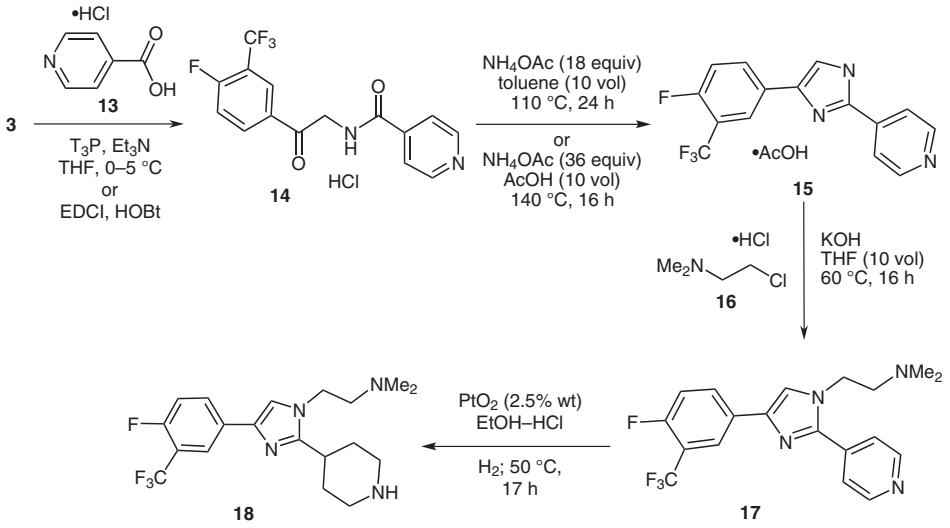


Figure 1 Impurities **11** and **12** observed during synthesis of **6**

Imidazole ring construction from ketoamides using ammonium acetate has been known in literature.[12] Thus, keeping the literature methods in view, synthesis of **15** was explored in various solvents with excess of ammonium acetate (Table 2). As determined by HPLC, the formation of **15** was successful in acetic acid, propanoic acid, and toluene. However, azeotropic removal of water was required in the synthesis of **15** using toluene as a solvent system. Based upon the yield data, we preferred acetic



Scheme 3 Synthesis of compound **18**

Table 1 A Solvent and Acid Activating Agents Screening Study in the Synthesis of **14**

Entry	Substrate	Acid activating reagent	Solvent	Base[a]	Temp (°C)	Yield (%)[b]
1	**13** acid chloride	none	CH_2Cl_2	Et_3N	25	30
2	**13** acid chloride	none	CH_2Cl_2	Et_3N	reflux	20
3	**13**	EDCI-HOBT	THF	NMM	23–30	88
4	**13**	T_3P in EtOAc	EtOAc–THF	Et_3N	0–5	79
5	**13**	T_3P in EtOAc	EtOAc–THF	NMM	0–5	75

[a] NMM: *N*-Methylmorpholine.
[b] Isolated yield.

acid as a solvent for the synthesis of **15** using ammonium acetate at 140 °C under pressure. This resulted in excellent conversion of **15** as determined by HPLC. The reaction workup involved addition of water effecting in crystallization of **15**. Thus, synthesis of **15** was demonstrated at 100 gram scale, which provided product in 89% yield with excellent purity.

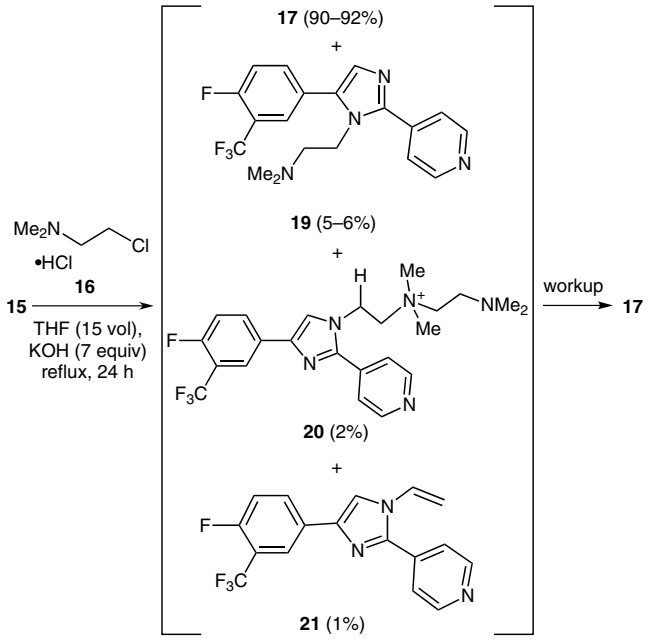
A screening study was performed to find a suitable experimental condition for N-alkylation of **15** with **16** (Table 3). Impact of organic and inorganic bases was studied. HPLC data from this study indicated that use of sodium hydride as a base in THF provided the best result with respect to the formation of **17** (Table 3). Both cesium carbonate and powdered potassium hydroxide provided similar outcome in the synthesis of **17**. As the use of NaH on large scale poses challenges with respect to safety and handling, we were interested in the development of a process with the use of alkali metal hydroxide. Thus, a study was further completed to find the optimum amount of potassium hydroxide required for the formation of **17** (Table 3, entries 9–14). Based upon the data in Table 3, alkylation of **15** using THF as a solvent and powdered KOH provided a mixture of **17** and **19** in ratio of 91:6 along with undesired impurities (**20** and **21**, Scheme 4). The possible pathway for the formation of **20** may involve the reaction of **17** with **16** to form quaternary salt **20**), which upon elimination under basic conditions leads to formation of **21** (Scheme 5).

Keeping the complexity of alkylation reaction in view, a workup involving treatment of reaction mixture with activated carbon followed by crystallization was designed to obtain pure compound **17** in 78% yield. Absorption of **19** was observed on the carbon and it was determined that 30% of carbon was required for removal of **19**. N-Alkylation of **15** was performed at 300 g scale, which provided **17** in 77% isolated yield with excellent purity.

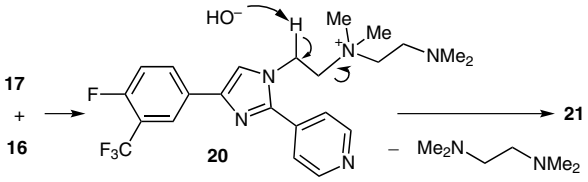
Table 2 A Solvent Screening Study in the Synthesis of **15**

Entry	NH_4OAc (equiv)	Solvent	Volume[a]	Temp (°C)	Time (h)	Formation of **15** by HPLC (%)	Yield (%)[b]
1	20	EtOH	20	reflux	24	20	NI
2	20	*i*-PrOH	20	reflux	24	32	NI
3	50	AcOH	20	110	24	57	NI
4	50	AcOH	20	140	10	94	NI
5	50	AcOH	10	140	10	91	NI
6	36	AcOH	10	140	12	91	NI
7	36	$EtCO_2H$	10	140	10	93	NI
8	36	AcOH	10	140	16	93	89
9	36	AcOH	10	140	16	94	90
10	20	AcOH	10	140	16	68	NI
11	12	AcOH	10	140	16	52	NI
12	21	toluene	21	111	24	86	78

[a] Reaction volume is based upon the quantity of **15** (g) used in the reaction, for example, for entry 9 amount of **15** used was 100 g (1 equiv); thus 10 solvent volumes correspond to 10 × 100 = 1 L; NI = product not isolated.
[b] Isolated yield.



Scheme 4 Impurities observed during **15** alkylation



Scheme 5 Possible pathway for the formation of impurity **21**

Our attempts to reduce the pyridine ring of **17** by catalytic hydrogenation using 5% palladium on carbon in acetic acid at room temperature and 50 psi gave a mixture of desired product **18** along with corresponding 4-des-fluoro analogue **22** (Figure 2) after 30 hours.[13]

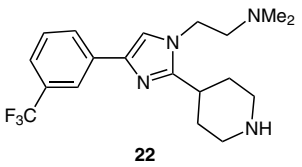
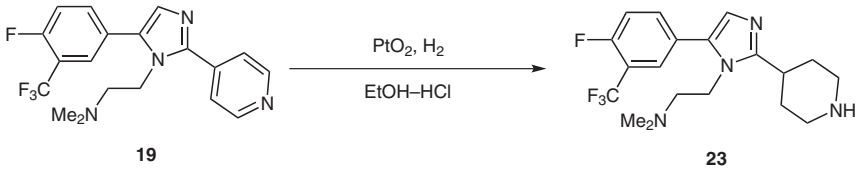


Figure 2 Structure of **22**

Table 3 Imidazole **25** N-Alkylation Screening Study and Optimized Conditions Data

Entry	Starting material and base (equiv)			Reaction conditions		In situ analysis of N-alkylation by HPLC[b]					Yield
	15	**16**	Base	Solvent (vol)[a]	Temp (°C), time (h)	**15** (%)	**17** (%)	**21** (%)	**19** (%)	**20** (%)	of **17** (%)
1	1	2	NaH (10.0)	THF (20)	63–65, 18	ND	94.1	2.1	1.05	0.8	80
2	1	2	DIPEA (3.5) K_2CO_3 (3.5)	DMF (20)	63–65, 18	52.4	35.4	0.3	10.1	0.3	NI
3	1	2	*t*-BuOK (7.0)	THF (20)	63–65, 18	56	–	–	–	–	NI
4	1	2	Cs_2CO_3 (7.0)	THF (20)	63–65, 18	ND	92.3	1.5	4.3	0.8	76
5	1	2	NaH (6.0)	THF (20)	63–65, 18	ND	82.2	1.8	13.1	0.5	66
6	1	2	powder KOH (7)	THF (20)	63–65, 18	ND	90.3	0.7	5.4	ND	77
7	1	2	flake KOH (7)	THF (20)	63–65, 18	0.03	91.5	1.7	5.42	0.8	75
8	1	2	powder NaOH (3)	DMSO (15)	60–65, 16	79.8	11.0	0.6	7.36	0.9	NI
9	1	2	powder KOH (7)	THF (15)	63–65, 18	ND	89.8	1.4	5.4	0.1	74
10	1	2	powder KOH (6)	THF (15)	63–65, 18	0.7	90.5	1.6	5.5	ND	74
11	1	2	powder KOH (5)	THF (15)	63–65, 18	0.7	87.3	1.9	7.9	0.4	73
12	1	2	powder KOH (4)	THF (15)	63–65, 18	46.4	30.4	2.6	15.7	1.7	NI
13	1	2	powder KOH (3)	THF (15)	63–65, 18	74.1	1.2	1.1	20.6	0.7	NI
14	1	2	powder KOH (6)	THF (15)	63–65, 18	0.6	92.1	1.0	6.4	0.6	77
15	1	2	Cs_2CO_3 (7.0)	THF (20)	63–65, 18	ND	91.2	0.6	4.8	0.3	74
16	1	2	powder KOH (6)	THF (15)	63–65, 18	0.6	92.1	1.0	6.4	0.6	77
17	1	2	powder KOH (6)	THF (15)	63–65, 18	0.8	89.1	0.6	6.7	0.3	77
1	1	2	NaH (10.0)	THF (20)	63–65, 18	ND	94.1	2.1	1.1	0.8	78

[a] Reaction volume is based upon the quantity of **15** (g) used in the reaction (as explained in footnote a of Table 2).
[b] ND: not detected.
[c] Isolated yield. NI: not isolated.



19 23

Scheme 6 Synthesis of **23**

Table 4 Hydrogenation of **17** Using PtO_2 Catalyst

Entry	Starting material and conditions					Temp (°C), time (h)	In situ analysis by HPLC (**18**; %)	Yield (%)[a]
	17 (g)	EtOH (L)	Catalyst	Concd HCl (mL)	H_2 (MPa)			
1	36	0.50	PtO_2 (5%)	21	1.4–1.6	48–52, 28	96.9	91
2	200	2.8	PtO_2 (2.5%)	105	1.4–1.6	48–52, 22	98.9	92

[a] Isolated yield.

However, we were successful in catalytic reduction of **17** using PtO_2 (2.5%) in ethanol under acidic conditions (Table 4).[14] Removal of catalyst by filtration followed by neutralization of reaction solution with sodium hydroxide provided **18** in good yield with excellent purity. In a similar fashion, isomer **23** was also prepared via hydrogenation of **19** (Scheme 6); the latter was obtained by chromatographic purification.

In conclusion, we have described a practical synthesis of 2-{4-[4-fluoro-3-(trifluoromethyl)phenyl]-2-(piperidin-4-yl)-1*H*-imidazol-1-yl}-*N*,*N*-dimethylethanamine.

^{1}H, ^{19}F, and ^{13}C NMR spectra were recorded in $CDCl_3$ using a Bruker Avance 400 MHz spectrometer. Chemical shifts (δ) are expressed in ppm downfield relative to TMS (0 ppm) and coupling constants (*J*) are given in Hz. Standard abbreviations are used to describe the signal patterns. High-resolution mass spectra (HRMS) were obtained using a Waters GCT Premier TOF mass spectrometer with EI source.

_N_-{2-[4-Fluoro-3-(trifluoromethyl)phenyl]-2-oxoethyl}isonicotinamide Hydrochloride (15)

The tosylate salt **3** (392 g, 1.00 mole) was combined with isonicotinic acid (135 g, 1.09 mol) and THF (5.5 L). The resultant slurry was cooled to 0–5 °C. T_3P (50% in EtOAc; 1001 g, 1.57 mol) diluted in THF (0.75 L) and Et_3N (510 g, 4.94 mol) diluted in THF (0.75 L) were added concurrently over 0.5 h to give a yellow, homogeneous solution (addition of T_3P solution was slightly faster than Et_3N). The reaction was quenched with brine (3 L) and the aqueous layer was back-extracted with EtOAc (0.5 L). The combined organic layers were washed with brine (2 × 3 L), dried ($MgSO_4$), filtered, and concentrated to give a yellow oil. The crude oil was dissolved in EtOAc (3 L), cooled to 5–10 °C, and HCl gas was bubbled in for 1 h. The resultant slurry was stirred at 15 °C for 2 h. The mixture was concentrated to 1.5 L, and MeOH (1.5 L) was added. The slurry obtained was stirred at r.t. for 6 h. The material was filtered and dried under vacuum; yield: 280 g (77%); yellow solid; purity: 99.2%; mp 117–119 °C.

^{1}H NMR (DMSO-d_6): δ = 4.87 (d, *J* = 5.3 Hz, 2 H), 7.73 (t, *J* = 9.7 Hz, 1 H), 7.78 (d, *J* = 5.7 Hz, 2 H), 8.35 (d, *J* = 7.0 Hz, 1 H), 8.43 (m, 1 H), 8.75 (d, *J* = 6.2 Hz, 2 H), 9.3 (t, *J* = 5.3 Hz, 1 H).

^{13}C NMR (DMSO-d_6): δ = 193.5, 165.6, 160.8, 150.8, 141.1, 136.0, 135.9, 132.3, 127.8, 121.7, 118.7, 118.4, 47.1.

^{19}F NMR (DMSO-d_6): δ = –60.3, –108.6.

HRMS: *m*/*z* calcd for $C_{15}H_{10}F_4N_2O_2$: 326.0678; found: 326.0668.

4-{4-[4-Fluoro-3-(trifluoromethyl)phenyl]-1*H*-imidazol-2-yl}pyridine Acetic Acid Salt (15)

Compound **15** (100 g, 0.276 mol) was combined with NH_4OAc (758 g, 9.83 mol) and AcOH (1 L) and the mixture was heated in an autoclave at 140 °C for 20 h. The mixture was concentrated to remove AcOH, and H_2O (2 L) was added. The mixture was stirred at 20 °C for 2 h. The material was filtered and washed with H_2O (0.5 L). The crude product was purified by reslurrying in EtOAc (0.5 L) and heptanes (1 L). The material was filtered and dried under vacuum; yield: 228 g (89%); brown solid; purity: 99.4%; mp 233–235 °C.

^{1}H NMR (DMSO-d_6): δ = 1.89 (s, 3 H), 7.54 (t, *J* = 9.7 Hz, 1 H), 7.92 (d, *J* = 6.2 Hz, 2 H), 8.10 (s, 1 H), 8.22 (d, *J* = 5.7 Hz, 2 H), 8.65 (d, *J* = 5.7 Hz, 2 H), 11.95 (s, 1 H), 13.22 (s, 1 H).

^{13}C NMR (DMSO-d_6): δ = 172.4, 159.2, 156.7, 150.8, 144.3, 140.0, 137.3, 131.9, 131.1, 123.0, 119.4, 118.1, 118.0, 117.4, 21.5.

^{19}F NMR (DMSO-d_6): δ = –60.0, –119.4.

HRMS: *m*/*z* calcd for $C_{17}H_{13}F_4N_3O_2$: 367.0944; found: 367.0941.

2-{4-[4-Fluoro-3-(trifluoromethyl)phenyl]-2-(pyridin-4-yl)-1*H*-imidazol-1-yl}-*N*,*N*-dimethylethanamine (17)

The imidazole **15** (192 g, 0.523 mol) was combined with KOH (176 g, 3.14 mol) and THF (3 L). The mixture was heated to 30–40 °C and stirred for 1 h. 2-Chloro-*N*,*N*-dimethylethanamine hydrochloride (**16**; 150 g, 1.04 mol) was added and the reaction mixture was heated at 60–65 °C for 20 h. The mixture was filtered and the cake washed with EtOAc (0.4 L). Activated carbon (30 wt%) was added to the filtrate and the mixture was stirred at 60–65 °C for 3 h. The mixture was filtered through Celite, and the cake rinsed with EtOAc (0.8 L). The filtrate was concentrated to a brown solid (175 g). The crude material was slurried in EtOAc (0.1 L) and heptanes (1 L) at r.t. for 16 h. The material was filtered and dried under vacuum; yield: 151.8 g (77%); yellow solid; purity: 99.3%; mp 122–126 °C.

^{1}H NMR (DMSO-d_6): δ = 2.07 (s, 6 H), 2.59 (t, *J* = 6.5 Hz, 2 H), 4.21 (t, *J* = 6.5 Hz, 2 H), 7.53 (t, *J* = 10.1 Hz, 1 H), 7.71 (dd, *J* = 4.4 Hz, 2 H), 8.12 (br t, 3 H), 8.70 (dd, *J* = 4.4 Hz, 2 H).

^{13}C NMR (DMSO-d_6): δ = 150.6, 145.3, 138.3, 138.0, 131.7, 131.6, 131.0, 130.9, 123.1, 118.2, 118.0, 59.2, 45.6, 45.5, 40.4.

^{19}F NMR (DMSO-d_6): δ = –60.1, –119.3.

HRMS: *m*/*z* calcd for $C_{19}H_{18}F_4N_4$: 378.1468; found: 3788.1462.

2-{4-[4-Fluoro-3-(trifluoromethyl)phenyl]-2-(pyridin-4-yl)-1*H*-imidazol-1-yl}-*N*,*N*-dimethylethanamine (18)

Compound **17** (143 g, 0.378 mol) was charged to an autoclave followed by EtOH (1.1 L). PtO_2 (2.5%) was added, followed by aq 2 N HCl (0.38 L, 0.755 mol). The mixture was stirred at 70 °C under 140 psi H_2 for 24 h. The mixture was filtered through Celite and the cake was rinsed with EtOH (2 × 0.25 L). The filtrate was concentrated to afford a white solid. The crude material was dissolved in H_2O (1.7 L) and EtOH (0.43 L) and cooled to 0–5 °C. By maintaining a temperature of 0–5 °C, the pH of the mixture was adjusted to 10–11 with aq 2 N NaOH. The resultant slurry was held at 0–5 °C for 2 h. The product was filtered, rinsed with cold EtOH–H_2O (1:5, 0.8 L), and dried under vacuum (60–70 °C); yield: 149 g (88%); white solid; purity: 99.0%; mp 92–95 °C.

^{1}H NMR (DMSO-d_6): δ = 1.70 (br q, 4 H), 2.17 (s, 6 H), 2.54 (m, 4 H), 2.81 (m, 1 H), 3.00 (d, J = 11.9 Hz, 2 H), 3.99 (t, J = 6.6 Hz, 2 H), 7.44 (t, J = 10.1 Hz, 1 H), 7.69 (s, 1 H), 8.01 (d, J = 7.0 Hz, 2 H).

^{13}C NMR (DMSO-d_6): δ = 32.32, 33.59, 43.08, 45.30, 46.08, 59.45, 116.38, 117.29, 117.40, 121.45, 124.15, 129.88, 132.11, 135.91, 152.21, 155.72, 158.19.

^{19}F NMR (DMSO-d_6): δ = –60.0, –120.6.

HRMS: m/z calcd for $C_{19}H_{24}F_4N_4$: 384.1937; found: 384.1929.

2-{5-[4-Fluoro-3-(trifluoromethyl)phenyl]-2-(pyridine-4-yl)-1*H*-imidazol-1-yl}-*N*,*N*-dimethylethanamine (19)

The active carbon cake containing crude **19** from the preparation of **17** was added to MeOH (1 L) and refluxed for 1 h. The material was filtered and the filtrate was concentrated to obtain 33 g of a red solid, which was purified by preparative HPLC; yield: 1.9 g; white solid; purity 98.2%; mp 157–161 °C.

^{1}H NMR (DMSO-d_6): δ = 2.18 (s, 6 H), 2.68 (t, J = 5.7 Hz, 2 H), 4.38 (t, J = 5.7 Hz, 2 H), 7.43 (t, J = 9.7 Hz, 1 H), 7.83 (s, 1 H), 8.11 (m, 4 H), 8.42 (d, J = 6.6 Hz, 2 H).

^{13}C NMR (DMSO-d_6): δ = 45.01, 55.66, 58.74, 116.42–117.34, 118.47, 121.87, 124.24, 130.08, 132.51, 133.24, 142.75, 147.95, 149.31, 155.49, 157.99.

^{19}F NMR (DMSO-d_6): δ = –60.0, –121.2.

HRMS: m/z calcd for $C_{19}H_{18}F_4N_4$: 378.1468; found: 378.1472.

2-{5-[4-Fluoro-3-(trifluoromethyl)phenyl]-2-(piperidin-4-yl)-1*H*-imidazol-1-yl}-*N*,*N*-dimethylethanamine (23)

Reduction of **19** using method outlined for compound **18** provided **23**; yield: 4.9 g (64%); white solid; purity: 99.6%; mp 166–169 °C.

^{1}H NMR (DMSO-d_6): δ = 1.71 (br q, 2 H), 1.84 (br d, J = 11.4 Hz, 2 H), 2.00 (d, J = 9.7 Hz, 2 H), 2.12 (s, 6 H), 2.33 (m, 4 H), 2.62 (m, 1 H), 2.90 (d, J = 11.0 Hz, 2 H), 7.43 (t, J = 9.7 Hz, 1 H), 7.65 (s, 1 H), 8.01 (d, J = 7.0 Hz, 2 H).

^{13}C NMR (DMSO-d_6): δ = 30.78, 35.56, 45.55, 53.47, 56.28, 56.86, 113.25, 117.14, 117.33, 121.45, 121.86, 121.90, 124.15, 130.03, 130.11, 132.37, 136.72, 152.13, 155.68, 158.17.

^{19}F NMR (DMSO-d_6): δ = –60.0, –120.7.

HRMS: m/z calcd for $C_{19}H_{24}F_4N_4$: 384.1937; found: 384.1907.

Acknowledgment

We are thankful to Dr. Mike Fogarty for providing analytical data. Professors M. Miller and W. Roush are acknowledged for thoughtful discussion and valuable suggestions.

References

(1) Fromtling, R. A. *Clin. Microbiol. Rev.* **1988**, *1*, 187.
(2) Sharpe, T. R.; Cherfolsky, S. C.; Hewes, W. E.; Smith, D. H.; Gregory, W. A.; Haber, S. B.; Leadbetter, M. R.; Whitney, J. G. *J. Med. Chem.* **1985**, *28*, 1188.
(3) Uçucu, Ü.; Gündoğdu, N.; Işikadağ, I. *Farmaco* **2001**, *56*, 285.
(4) Graczyk, P. P.; Khan, A.; Bhatia, G. S.; Palmer, V.; Medland, D.; Numata, H.; Oinuma, H.; Catchick, J.; Dunne, A.; Ellis, M.; Smales, C.; Whitfield, J.; Neame, S. J.; Sha, B.; Whilton, D.; Morgan, L.; Patel, T.; Chung, R.; Desmond, D.; Staddon, J. M.; Sato, N.; Inoue, A. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4664.
(5) Laufer, S. A.; Zimmermann, W.; Ruff, J. *J. Med. Chem.* **2004**, *47*, 6311.
(6) Black, J. W.; Durant, G. I.; Emmett, J. C.; Ganellin, C. R. *Nature* **1974**, *248*, 65.
(7) Srinivas, N.; Palne, S.; Nishi; Gupta, S.; Bhandari, K. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 324.
(8) Kiselyov, A. S.; Semenova, M.; Semenov, V. V. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 1440.
(9) Blum, C. A.; Zheng, X.; DeLombaert, S. *J. Med. Chem.* **2004**, *47*, 2318.
(10) For leading references, see: (a) Jin, Z. *Nat. Prod. Rep.* **2009**, *26*, 382. (b) Jin, Z. *Nat. Prod. Rep.* **2006**, *23*, 464. (c) Jin, Z. *Nat. Prod. Rep.* **2005**, *22*, 196. (d) Cui, B.; Zheng, B. L.; He, K.; Zheng, Q. Y. *J. Nat. Prod.* **2003**, *66*, 1101.
(11) Shepherd, T. A.; Dally, R. D.; Joseph, S. US Patent 120801 A1, **2010**.
(12) (a) Bellina, F.; Rossi, R. *Adv. Synth. Catal.* **2010**, *352*, 1; and references cited therein. (b) Zuliana, V.; Cocconcelli, G.; Fantini, M.; Ghiron, C.; Rivara, M. *J. Org. Chem.* **2007**, *72*, 4551.
(13) Jennings, L. D.; Foreman, K. W.; Rush, T. S.; Tsao, D. H. H.; Mosyak, L.; Kincaid, S. L.; Sukhdeo, M. N.; Sutherland, A. G.; Ding, W.; Kenny, C. H.; Sabus, C. L.; Liu, H.; Dushhin, E. G.; Moghazeh, S. L.; Labthavikul, P.; Peterse, P. J.; Tuckman, M.; Ruzin, A. V. *Bioorg. Med. Chem.* **2004**, *12*, 5115.
(14) Phillips, J. G.; Jaworska, M.; Lew, W. *Synthesis* **2010**, 71.

