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Synthesis of Fluorinated 1-(3-Morpholin-4-yl-phenyl)-Ethylamines

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Abstract—The synthesis of four (±)-fluorinated 1-(3-morpholin-4-yl-phenyl)-ethylamines and an enantioselective approach to these amines through reductive amination are described.

Substituted 1-phenylethylamines are ubiquitous building blocks for amide formation and reductive alkylation in medicinal chemistry programs. These amines have been incorporated into numerous drug candidates such as CP-544372 (Fig. 1)[1] a macrolide antibiotic with activity against both macrolide-susceptible and MLS_B-resistant organisms, and H 409/22 (Fig. 1),[2] a NPY antagonist in phase II clinical trial for the treatment of cardiovascular disorders. In a recent medicinal chemistry program, we introduced a morpholine moiety into the *meta* position of 1-phenylethylamine, and the resulting 1-(3-morpholin-4-yl-phenyl)ethylamine (**1**) was used in an amide library synthesis. It was found that the incorporation of the morpholine moiety resulted in both improved solubility and pharmacokinetic properties. As introduction of fluorine into biologically active compounds can profoundly alter their chemical, physical, and biological properties,[3] we were interested in the fluorinated analogues of **1**. Simultaneous introduction of both morpholine and fluorine into the phenyl ring of Linezolid (Fig. 1), a new antibacterial agent, has been shown to provide improved safety profiles over previously identified oxazolinone antibacterials.[4] This report describes the synthesis of four (±)-fluorinated 1-(3-morpholin-4-yl-phenyl)ethylamines, **2**, **3**, **4**, and **5** as well as an enantioselective approach to these amines (Fig. 2).

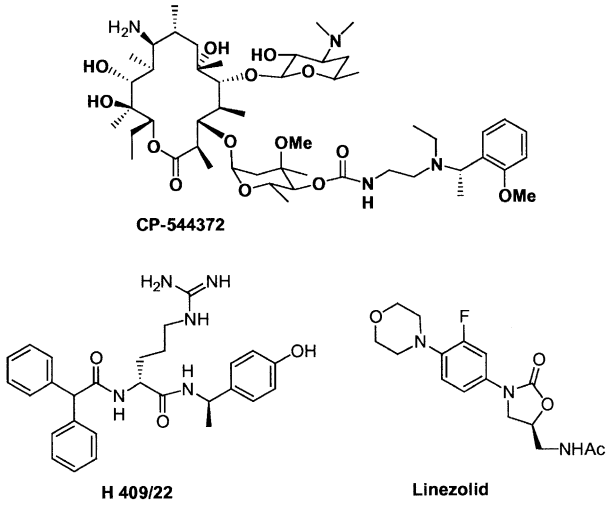

Figure 1.

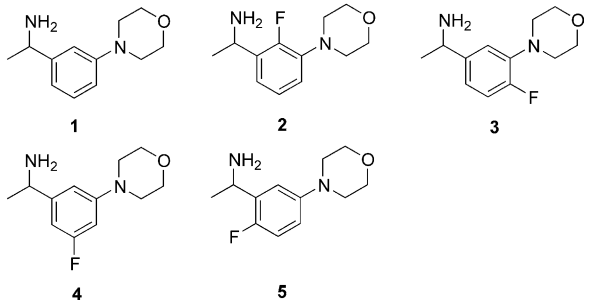

Figure 2.

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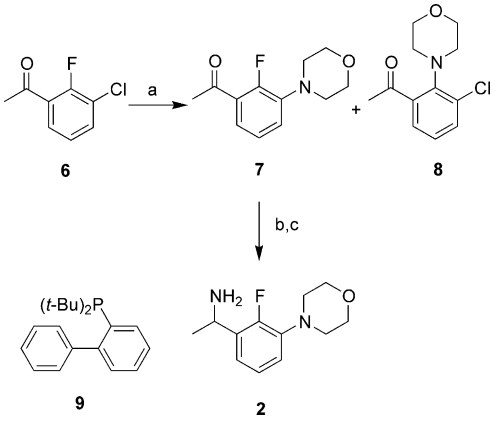
Fluoro amine **2** was prepared from 2-fluoro-3-chloroacetophenone (**6**)[5] in three steps using the palladium-catalyzed amination conditions that we recently developed for 4-fluoro-3-bromo-acetophenone (Scheme 1).[6] Reaction of **6** with morpholine was sluggish using $Pd(OAc)_2$ and ligand **9** in the presence of Cs_2CO_3 in benzene under reflux, while the same reaction using NaO*t*Bu as a base afforded a 20:1 mixture of the fluoride **7** and the chloride **8** as shown by LC–MS analysis of the crude product. Under the latter conditions, no products resulting from the palladium-catalyzed α-arylation of the acetyl group were observed.[7] Compound **7** was obtained in 73% yield after purification of the crude product through silica gel flash chromatography. Oxime formation followed by reduction afforded fluoro amine **2**.

The synthesis of fluoro amine **3** is outlined in Scheme 2. The commercially available 4-fluoro-acetophenone (**10**) was nitrated with concentrated sulfuric acid and fuming nitric acid to give compound **11**,[8] which was reduced selectively to amine **12** through hydrogenation using sulfided platinum on carbon [Pt(S)/C] as catalyst.[9] Our attempts to convert the amine in **12** into the morpholine ring using bromoethyl ether were unsuccessful under a variety of basic conditions, and the failure of this cyclization presumably results from the reduced basicity of the amine in **12** due to the presence of two electron-withdrawing groups: acetyl group and fluorine at *meta* and *ortho* positions, respectively. With this in mind, we then reduced ketone **12** to alcohol **13** using sodium borohydride. As we had hoped, compound **13**, upon treatment with bromoethyl ether in the presence of diisopropylethylamine, underwent smooth cyclization to give *N*-aryl morpholine **14**. This compound was converted to azide **15** using diphenylphosphoryl azide,[10] and reduction of the azide generated fluoro amine **3**.



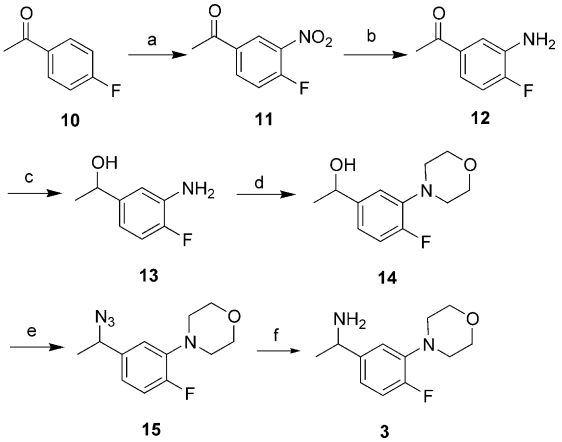
Scheme 1. (a) Morpholine (1.5 equiv), $Pd(OAc)_2$ (15 mol% Pd), **9** (30 mol%), NaO*t*Bu, toluene, 80 °C, 0.5 h, 73%; (b) $NH_2OH{\cdot}HCl$, Et_3N, EtOH, 25 h; (c) H_2, Ra–Ni, 30% $NH_3{\cdot}H_2O$ in MeOH, 100% over two steps.

We subsequently developed a shorter route to fluoro amine **3** using the palladium-catalyzed amination that we recently reported (Scheme 3).[6] Bromide **16**, upon treatment with morpholine in the presence of $Pd(OAc)_2$ and ligand **9** using Cs_2CO_3 as a base in benzene under reflux, furnished fluoride **17** in 80% yield. The transformation from acetophenone **17** to fluoro amine **3** was carried out through reduction of the oxime.

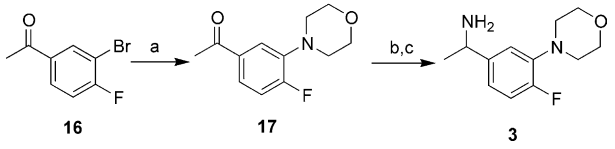
Scheme 4 depicts the synthesis of fluoro amine **4**. Exposure of 3,5-difluoro-acetophenone (**18**) to morpholine in the presence of potassium carbonate brought about the facile nucleophilic substitution of the fluorine,[11] and the resulting *N*-aryl morpholine **19** was converted to fluoro amine **4**.

The synthesis of fluoro amine **5** was carried out in a five-step sequence (Scheme 5). Regioselective nitration of 2-fluoroacetophenone (**20**) and reduction of the resulting nitro compound **21** furnished amine **22**. In contrast with its 4-fluoro counterpart **12** (Scheme 2), the 6-fluoro amine **22** underwent clean cyclization with bromoethyl ether in the presence of diisopropylethylamine to afford *N*-aryl morpholine **23**. Conversion of **23** to fluoro-amine **5** was carried out in a straightforward fashion.

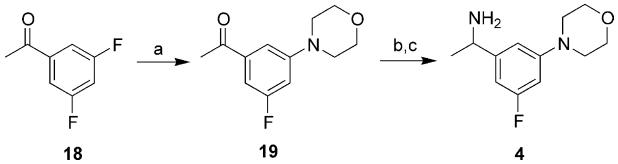
Next, we explored the asymmetric synthesis of (*S*)-**3** from acetophenone **17** (Scheme 3) through reductive amination with (*S*)-1-phenylethylamine.[12] Imine **24** was formed cleanly using $TiCl_4$ as a Lewis acid and a dehydration



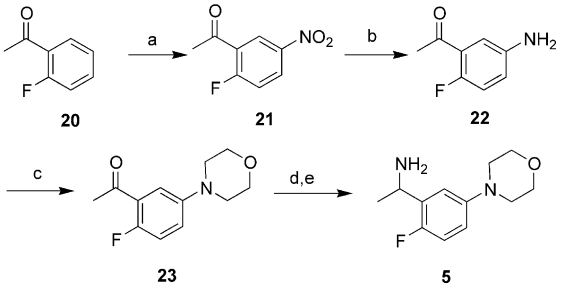
Scheme 2. (a) Concd H_2SO_4, fuming HNO_3, −15 °C, 79%; (b) H_2 (50 psi), Pt(S)/C, EtOH, 80%; (c) $NaBH_4$, MeOH, CH_2Cl_2, 99%; (d) bromoethyl ether, *i*-Pr_2NEt, toluene, 110 °C, 87%; (e) $Ph_2P(O)N_3$, DBU, 0 °C, 90%; (f) $LiAlH_4$, THF, −40 °C, 99%.



Scheme 3. (a) Morpholine (4 equiv), $Pd(OAc)_2$ (10 mol% Pd), **9** (10 mol%), Cs_2CO_3, benzene, 80 °C, 17 h, 79%; (b) $NH_2OH{\cdot}HCl$, Et_3N, EtOH, 72 h; (c) H_2, Ra–Ni, 30% NH_3H_2O in MeOH, 75% over two steps.



Scheme 4. (a) Morpholine, K_2CO_3, 150 °C, 72 h, 48%; (b) $NH_2OH{\cdot}HCl$, Et_3N, EtOH, 72 h; (c) H_2, Ra–Ni, 30% $NH_3{\cdot}H_2O$ in MeOH, 74% over two steps.



Scheme 5. (a) Concd H_2SO_4, fuming HNO_3, −15 °C, 55%; (b) H_2 (50 psi), Pt(*S*)/C, EtOH, 57%; (c) bromoethyl ether, *i*-Pr_2NEt, toluene, 110 °C, 73%; (d) $NH_2OH{\cdot}HCl$, Et_3N, EtOH, 72 h; (d) H_2, Ra–Ni, 30% $NH_3{\cdot}H_2O$ in MeOH, 84% over two steps.

agent, and hydrogenation of the crude imine **24** with Raney nickel provided the secondary amine (*S*,*S*)-**25** in 92% de as shown by HPLC analysis. The same diastereoselectivity was obtained when the reduction was carried out with sodium borohydride in methanol at −78 °C. At room temperature, however, the same reduction gave only 72% de.

Subsequent hydrogenolytic cleavage of the crude bis-phenylethylamine **25** (92% de) with ammonium formate and Pd/C[13] occurred adjacent to the less substituted phenyl ring, and (*S*)-**3** was obtained exclusively in 92% ee. The optical purity was determined after derivatization with benzyl chloroformate and chiral HPLC analysis of the carbamtes. The crude hydrogenation product was treated with hydrogen chloride in ether, and the resulting dihydrochloride salt was recrystallized from acetone/H_2O/hexanes (20:4:1). The racemate was obtained as crystals, and the mother liquid was concentrated to give (*S*)-**3** dihydrochloride in 71% yield and >99% ee. The absolute configuration of (*S*)-**3** was confirmed by X-ray diffraction analysis of its dihydrochloride hydrate (Fig. 3, Scheme 6).

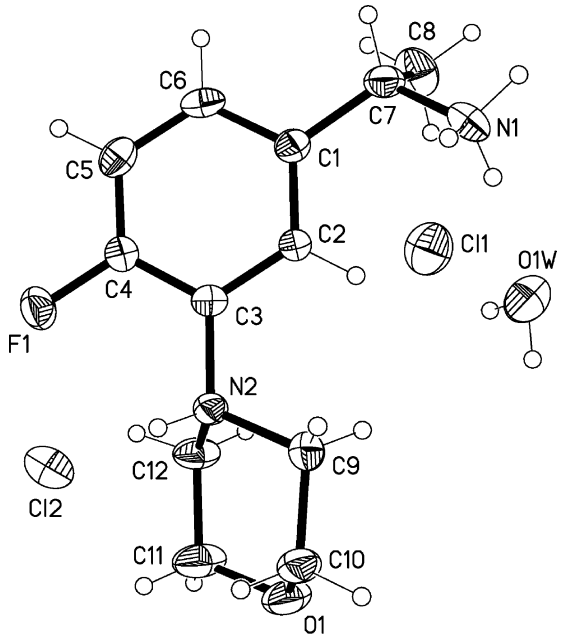
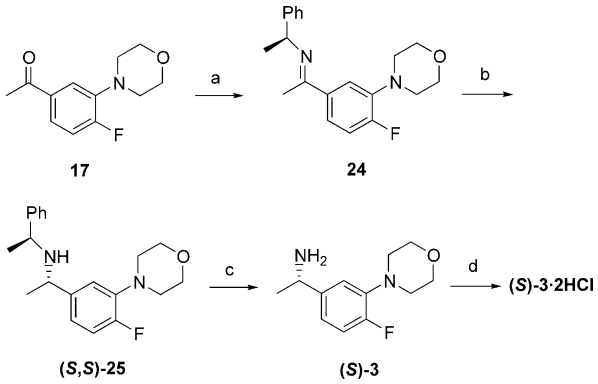


Figure 3. Thermal ellipsoid plot (35% ellipsoids) of crystalline (*S*)-**3**·2HCl·H_2O.



Scheme 6. (a) (*S*)-1-Phenylethylamine, $TiCl_4$, Et_3N, toluene, 12 h; (b) H_2 (30 psi), MeOH, Ra–Ni, 2 h, 92% de, 99%; (c) $HCOONH_4$, Pd/C, MeOH, 92% ee, 93%; (d) HCl in ether, >99% ee, 71% after recrystallization.

The methodology developed for the synthesis of (*S*)-**3** should be applicable to the preparation of (*R*)-**3** and the individual enantiomers of **2**, **4**, and **5** starting from appropriate chiral 1-phenylethylamines and fluorinated acetophenones.

In summary, we have synthesized four (±)-fluorinated 1-(3-morpholin-4-yl-phenyl)ethylamines and developed an enantioselective approach to these amines through reductive amination.[14] We anticipate these fluorinated amines to be versatile intermediates for medicinal chemistry programs.

Acknowledgements

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14. All new compounds have spectral and analytical data in agreement with the indicated structures. Compound **2**: ^{1}H NMR (400 MHz, CD_3OD) δ 1.63 (3H, d, $J=6.8$ Hz), 3.29 (4H, m), 3.90 (4H, m), 4.75 (1H, q, $J=6.8$ Hz), 4.88 (2H, s), 7.26–7.35 (3H, m); ^{13}C NMR (100 MHz, CD_3OD) δ 19.75, 46.14 (d, $J=6$ Hz), 53.17 (2C), 67.35 (2C), 122.06, 123.58, 126.83 (d, $J=4$ Hz), 127.86 (d, $J=12$ Hz), 139.17 (d, $J=11$ Hz), 154.43 (d, $J=247$ Hz). Compound **3**: ^{1}H NMR (400 MHz, CD_3OD) δ 1.33 (3H, d, $J=6.8$ Hz), 3.05 (4H, m), 3.81 (4H, m), 3.98 (1H, q, $J=6.8$ Hz), 4.83 (2H, s), 6.92–7.03 (3H, m); ^{13}C NMR (100 MHz, CD_3OD) δ 25.43, 52.04, 52.27 (2C), 68.10 (2C), 116.88 (d, $J=21$ Hz), 117.76 (d, $J=3$ Hz), 121.18 (d, $J=8$ Hz), 141.18 (d, $J=9$ Hz), 144.87, 156.02 (d, $J=242$ Hz). Compound **4**: ^{1}H NMR (400 MHz, CD_3OD) δ 1.36 (3H, d, $J=6.4$ Hz), 3.06 (4H, m), 3.79 (4H, m), 4.26 (1H, q, $J=6.4$ Hz), 4.83 (2H, s), 6.81 (1H, m), 6.91 (1H, dd, $J=9.2$, 8.8 Hz), 7.03 (1H, dd, $J=3.2$, 6.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 24.2, 46.4 (d, $J=10$ Hz), 51.6 (2C), 68.1 (2C), 115.9, 116.6 (d, $J=20$ Hz), 117.1 (d, $J=10$ Hz), 135.0 (d, $J=10$ Hz), 149.8, 156.05 (d, $J=230$ Hz). Compound **5**: ^{1}H NMR (400 MHz, CD_3OD) δ 1.37 (3H, d, $J=6.8$ Hz), 3.07 (4H, m), 3.80 (4H, m), 4.27 (1H, q, $J=6.8$ Hz), 4.84 (2H, s), 6.81 (1H, m), 6.92 (1H, t, $J=9.2$ Hz), 7.03 (1H, dd, $J=2.8$, 6.4 Hz); ^{13}C NMR (100 MHz, CD_3OD) δ 24.11, 46.45 (d, $J=3$ Hz), 51.60 (2C), 68.07 (2C), 115.92 (d, $J=4$ Hz), 116.62 (d, $J=23$ Hz), 117.18 (d, $J=9$ Hz), 134.74 (d, $J=14$ Hz), 149.83, 156.05 (d, $J=235$ Hz). Compound **7**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.63 (3H, d, $J=5.2$ Hz), 3.09 (2H, m), 3.88 (2H, m), 7.12 (2H, m), 7.43 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 31.6, 51.2 (2C), 67.0 (2C), 123.2, 124.3 (d, $J=10$ Hz), 126.9, 127.0, 140.8 (d, $J=10$ Hz), 155.6 (d, $J=260$ Hz), 196.6.