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Synthesis of monofluorinated 1-(naphthalen-1-yl)piperazines

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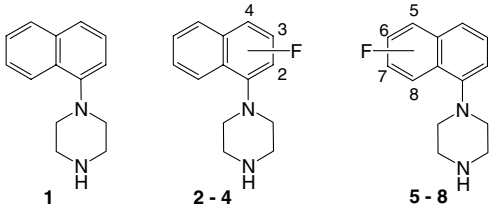
Abstract—A series of regioisomerically monofluorinated 1-(naphthalen-1-yl)piperazines is described.

4-Arylpiperazines are considered 'privileged' templates in drug discovery.[1] This core structure is found in numerous biologically active compounds and drugs, which act by various mechanisms for diverse indications. Foremost among these is their activity against monoamine based GPCRs, namely, dopaminergic,[2] serotonergic,[3] and adrenergic[4] GPCRs. Subtle structural changes of the arylpiperazine moiety in a lead molecule are often desired in order to optimize the potency and selectivity against these receptors and modulate the physical and ADME (absorption, distribution, metabolism, and elimination) properties of the molecule. The incorporation of fluorine into a lead molecule can alter its chemical properties (Pauling electronegativity of fluorine is 3.98 vs 2.20 for hydrogen), pharmacokinetic and pharmacodynamic properties (metabolic stability and absorption), and biological activity.[5a] It has been recognized that fluorine substitution on aromatic rings can be used to redirect metabolism while often preserving or improving receptor binding of medicinal compounds.[5b] Furthermore, aromatic fluorine atoms can participate in hydrogen bonding interactions.[5c] Therefore, fluoroaromatic piperazines are highly desirable intermediates for the synthesis of new drug candidates.

We describe herein the synthesis of a series of monofluorinated 1-(naphthalen-1-yl)piperazines (**1**), including 2-fluoronaphthalen-1-yl (**2**), 3-fluoronaphthalen-1-yl (**3**), 4-fluoronaphthalen-1-yl (**4**), 5-fluoronaphthalen-1-yl (**5**), 7-fluoronaphthalen-1-yl (**7**), and 8-fluoronaphthalen-1-yl piperazines (**8**).[6a,b] While the 6- and 7-fluoronaphthalen-1-yl piperazines (**6** and **7**) have been disclosed previously,[7a–c] we report the details of a more regioselective synthesis of intermediates leading to **7** (Scheme 5). The known methods for the preparation of arylpiperazines include reacting arylamines with bis(2-chloro-2-ethyl)amine[8a] or amination of aryl halides or triflates with monoprotected piperazine under Buchwald–Hartwig–Migita cross-coupling conditions.[8b–d] Selection of these techniques in combination with preparation of various functionalized fluoronaphthyl intermediates provided routes to the complete set of monofluorinated 1-(naphthalen-1-yl)piperazines **2**–**8**.



The synthesis of 1-(2-fluoronaphthalen-1-yl)piperazine[6a,b] (**2**) began with selective bromination of naphthalen-2-amine (**9**) at the 1-position to give **10** (Scheme 1).[9] Diazotization of amine **10** in the presence of fluoroboric acid provided the intermediate diazonium salt, which was isolated and subjected to thermal decomposition to yield the desired 1-bromo-2-fluoronaphthalene (**11**). Amination of the bromide **11** with Boc-piperazine followed by deprotection of the Boc group with trifluoroacetic acid provided **2** as the TFA salt.

In a manner similar to that described by Adcock and Dewar,[10] the synthesis of 1-(3-fluoronaphthalen-1-yl)piperazine (**3**) commenced with the diazotization of

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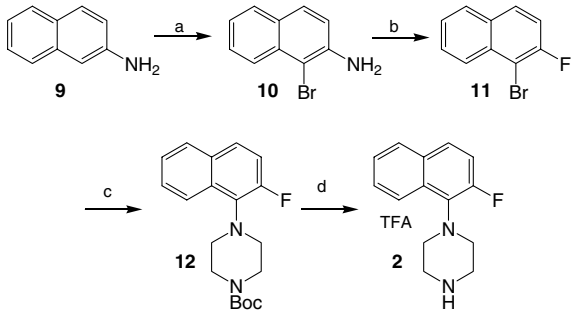
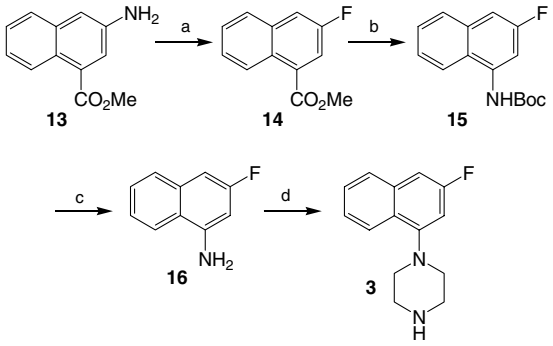


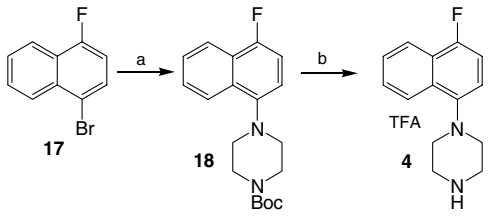
Scheme 1. Reagents and conditions: (a) NBS, DMF, 110 °C, 70%; (b) HBF_4, $NaNO_2$, THF, $NaBF_4$; xylenes, reflux, 1 h, 47%; (c) $Pd(OAc)_2$, NaO^{t}Bu, 2-(dicyclohexylphosphino)biphenyl, Boc-piperazine, toluene, 80 °C, 40%; (d) TFA, CH_2Cl_2, 0 °C, 40%.

methyl 3-amino-1-naphthoate (**13**) in the presence of fluoroboric acid to give methyl 3-fluoro-1-naphthoate (**14**) (Scheme 2). Hydrolysis of the ester followed by Curtius rearrangement of the acid and trapping of the resultant isocyanate with *t*-butanol afforded the Boc-protected naphthylamine **15**. Removal of the Boc group with trifluoroacetic acid provided 3-fluoronaphthalen-1-amine (**16**). Finally, the piperazine was constructed by reacting amine **16** with bis(2-chloro-2-ethyl)amine to give **3**.

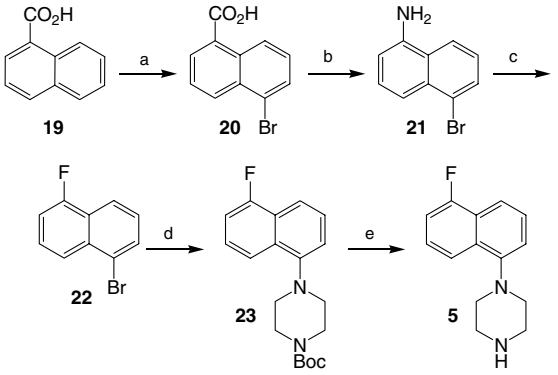
A facile route to 1-(4-fluoronaphthalen-1-yl)piperazine (**4**) is shown in Scheme 3. *N*-Arylation of Boc-piperazine with commercially available 1-bromo-4-fluoronaphthalene (**17**, Aldrich) yielded **18** and subsequent Boc cleavage with 50% TFA in dichloromethane gave **4** in 78% yield over two steps.



Scheme 2. Reagents and conditions: (a) 48% HBF_4, $NaNO_2$, THF, $NaBF_4$; PhCl, reflux, 1 h, 50%; (b) (1) 2 N KOH, MeOH, reflux, 2 h, 98%; (2) DPPA, Et_3N, ^{t}BuOH, 87%; (c) TFA, CH_2Cl_2, 33%; (d) bis-(2-chloro-2-ethyl)amine hydrochloride, $^i Pr_2EtN$, PhCl, 150 °C, 12%.



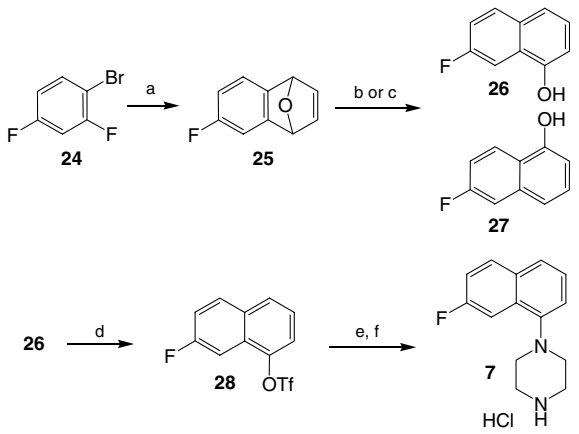
Scheme 3. Reagents and conditions: (a) $Pd(OAc)_2$, NaO^{t}Bu, 2-(dicyclohexylphosphino)biphenyl, Boc-piperazine, toluene, 80 °C; (b) TFA/CH_2Cl_2, 50:50, 0–25 °C, 1 h, 78% two steps.



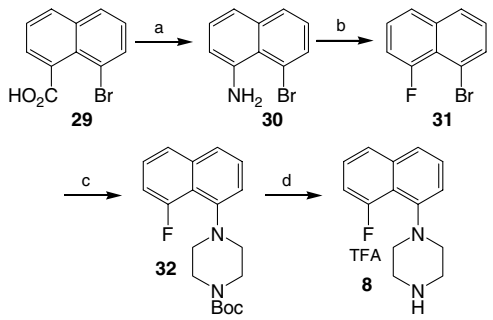
Scheme 4. Reagents and conditions: (a) Br_2, HOAc, 110 °C, 62%; (b) (1) ^{t}BuOH, Et_3N, DPPA; 2. TFA, 58%; (c) 48% HBF_4, $NaNO_2$, THF; $NaBF_4$, 47%; (d) $Pd(OAc)_2$, NaO^{t}Bu, 2-(dicyclohexylphosphino)biphenyl, Boc-piperazine, toluene, 80 °C; (e) 6 N HCl, 66% two steps.

The synthesis of 1-(5-fluoronaphthalen-1-yl)piperazine (**5**) is shown in Scheme 4. Naphthalene-1-carboxylic acid (**19**) was brominated with a degree of regioselectivity at the 5-position giving **20** as an easily isolable solid.[11] From this acid, Tagat et al. formed the *t*-butyl ester and converted the bromine to a fluorine via a halogen–metal exchange followed by quenching with an electrophilic fluorinating agent. Instead, by analogy with chemistry in Scheme 2, we converted carboxylic acid **20** to amine **21**, which was subsequently diazotized in the presence of fluoroboric acid to give the fluoro derivative **22**. Finally, amination of **22** with Boc-piperazine provided **23**, which following deprotection gave **5**.

The synthesis of 1-(7-fluoronaphthalen-1-yl)piperazine (**7**) from 7-fluoronaphthyl triflate (**28**) (prepared from 7-fluorotetralone) has been disclosed.[7c] Another route to 7-fluoronaphthalen-1-ol (**26**) (albeit without experimental detail)[12a] was via acid catalyzed opening of 7-fluoro-1,4-epoxy-1,4-dihydronaphthalene (**25**). To expedite the synthesis of **7**, we desired to improve the ring opening of **25** to the prerequisite 7-fluoronaphthalen-1-ol (**26**). Compound **25** was obtained from the Diels–Alder cyclization of furan with the benzyne intermediate generated from 1-bromo-2,4-difluorobenzene (**24**) (Scheme 5) similar to the method of Caster et al.,[12b] except that we used magnesium (THF, reflux) instead of *n*-BuLi (diethyl ether, −78 °C) to generate the benzyne intermediate. Acid catalyzed openings of the 1,4-epoxy bridge of 1,4-epoxy-1,4-dihydronaphthalene like **25** to a naphthol are known[12c] and substituent directed regioselectivity have been observed.[12d] We desired to find conditions to effect a regioselective opening of the 1,4-epoxy bridge in **25** to give the desired 7-fluoro isomer **26**. Initially, we found that treatment of **25** with concentrated HCl/ethanol at reflux gave a 2:1 mixture of the 7- and 6-fluoronaphthalen-1-ols (**26** and **27**) respectively. However, we discovered that the opening could be directed by use of BF_3-etherate in dichloromethane giving a 56% yield of the 7-fluoro isomer **26** in 95% regioisomeric purity. Naphthol **26** was converted to triflate **28** and then



Scheme 5. Reagents and conditions: (a) Mg/THF, furan, 2 h, 65 °C, 15 h, 97%; (b) concentrated HCl/ethanol, reflux, 2 h, 68%; (c) $BF_3{\cdot}OEt_2$, CH_2Cl_2, 0 °C to rt, 1.5 h, 60%; (d) Et_3N, Tf_2O CH_2Cl_2, rt, 1 h, 99%; (e) 0.1 equiv $Pd(OAc)_2$, 1.5 equiv NaO^{t}Bu, 0.12 equiv 2-(dicyclophosphino)biphenyl, 1.5 equiv Boc-piperazine, toluene, 85 °C, 3 h, 80%; (f) HCl (gas), CH_2Cl_2, rt, 3 h, 96%.



Scheme 6. Reagents and conditions: (a) H_2SO_4, NaN_3, $CHCl_3$, 40 °C, 96%; (b) 48% HBF_4, $NaNO_2$, THF; $NaBF_4$, 69%; (c) $Pd(OAc)_2$, NaO^{t}Bu, 2-(dicyclohexylphosphino)biphenyl, Boc-piperazine, toluene, 80 °C, 38%; (d) TFA, CH_2Cl_2, 0 °C, 89%.

coupled to Boc-piperazine under Buchwald–Hartwig–Migita conditions to give **7** after deprotection of the Boc group.

The synthesis of 1-(8-fluoronaphthalen-1-yl)piperazine (**8**) (Scheme 6) was analogous to the synthesis of **5** (Scheme 4), except that the starting 1-bromo-8-naphthoic acid (**29**),[†] was commercially available. Carboxylic acid **29** was converted to amine **30** via a Curtius rearrangement using sodium azide and sulfuric acid. Diazotization followed by fluorination of the diazonium salt with fluoroboric acid provided the requisite 1-bromo-8-fluoronaphthalene (**31**), which was coupled with Boc-piperazine under Buchwald–Hartwig–Migita conditions to give **32**. Finally acidic deprotection with trifluoroacetic acid afforded 1-(8-fluoronaphthalen-1-yl)-piperazine (**8**).

[†] 1-Bromo-8-naphthoic acid, CO-0063, Carbocore Research Chemicals and Intermediates.

In summary, a collection of monofluorinated 1-(naphthalen-1-yl)piperazines **2**–**8** were prepared as templates for drug discovery from a variety of routes and starting materials.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.05.156.

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