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Synthesis of fluorinated 1,8-naphthyridinone derivatives

Joseph T. Repine,[a,*] Douglas S. Johnson,[a,*] Timothy Stuk,[a] Andrew D. White,[a] Michael A. Stier,[a] Tingsheng Li,[b] Zhixiang Yang[b] and Samarendra N. Maiti[b]

[a]*Pfizer Global Research and Development, 2800 Plymouth Road, Ann Arbor, Michigan 48105, USA*
[b]*Naeja Pharmaceuticals, 4290-91a Street, Edmonton, Alberta, Canada T6E 5V2*

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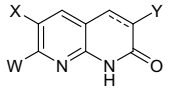
Abstract—Processes for the synthesis of fluorinated 1,8-naphthyridinone derivatives including 6,7-difluoro-1,8-naphthyridin-2-one are described.

The 1,8-naphthyridine core is a versatile template for drug discovery. This structure is incorporated in numerous biologically active compounds and drugs which act by various mechanisms for diverse indications. Among these are compounds useful as antibacterials,[1] anticonvulsants,[2] antihypertensives,[3] and inhibitors of both ACAT[4] and platelet aggregation.[5] Compounds containing the 1,8-naphthyridin-2(1*H*)-one (**1**) skeleton can illicit phosphodiesterase[6] and kinase activities[7] which have been indicated as treatments for asthma, proliferative and inflammatory disorders. In our laboratory, the 1,8-naphthyridin-2(1*H*)-one fragment has provided compounds which are potentially useful for the treatment of schizophrenia and bipolar disorder.[8]

From the above examples, structural changes surrounding a lead molecule with a 1,8-naphthyridine core are often desired in order to optimize the potency and selectivity against 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 versus 2.20 for hydrogen), pharmacokinetic and pharmacodynamic properties (metabolic stability and absorption), and biological activity.[9a] 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.[9b] Furthermore, aromatic fluorine can participate in hydrogen bonding interactions.[9c] An example of a drug containing a fluoro substituted naphthyridine core is the fluoroisoquinolone antibiotic enoxacin. Therefore, the incorporation of fluorine in a variety of naphthyridines would be expected to provide highly desirable intermediates for the synthesis of new drug candidates.

We describe herein the synthesis of a series of fluorinated 1,8-naphthyridinone fragments including 6-fluoro-7-(4-hydroxybutoxy)-3,4-dihydro-1,8-naphthyridin-2(1*H*)-one (**2**), 6-fluoro-7-(4-hydroxybutoxy)-1,8-naphthyridin-2(1*H*)-one (**3**), 3-fluoro-7-(4-hydroxybutoxy)-1,8-naphthyridin-2(1*H*)-one (**4**), and 6,7-difluoro-1,8-naphthyridin-2(1*H*)-one (**5**).



Cmpd.	W	X	Y	----
1	H	H	H	unsat.
2	$HO(CH_2)_4O$	F	H	sat.
3	$HO(CH_2)_4O$	F	H	unsat.
4	$HO(CH_2)_4O$	H	F	unsat.
5	F	F	H	unsat.

The synthesis of 6-fluoro-dihydronaphthyridinone analog **2** began with the synthesis of intermediate **10** as shown in Schemes 1 and 2. Regioselective displacement of the 6-chloro of 2,6-dichloro-5-fluoronicotinonitrile (**6**) by the alkoxide formed from 4-benzyloxy-1-butanol (**7**) proceeded in good yield to give **8**. This was the same regiochemical preference as observed by

* Corresponding authors. E-mail addresses: aarepinej@comcast.net; doug.johnson@pfizer.com

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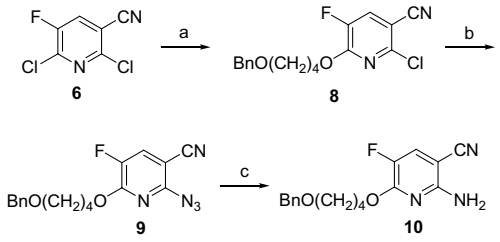
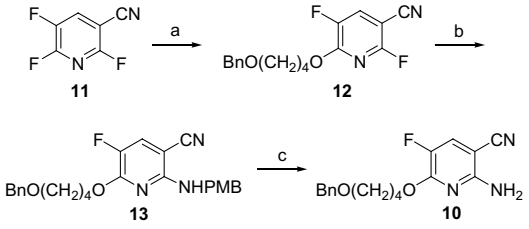


Scheme 1. Reagents and conditions: (a) $BnO(CH_2)_4OH$ (**7**), *t*-BuOK, THF, −78 °C to rt, 3 h, 70–80%; (b) NaN_3, DMF, 70 °C, 84%; (c) $(Me_3Si)_2S$, MeOH, rt, 86%.



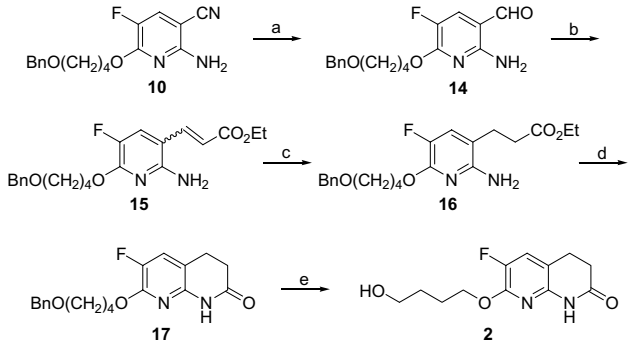
Scheme 2. Reagents and conditions: (a) $BnO(CH_2)_4OH$ (**7**), *t*-BuOK, THF, −70 °C to −50 °C, 1 h, reaction mixture carried to next step; (b) *p*-methoxybenzylamine, −70 °C to rt, 70% over two steps; (c) TFA, −8 °C to rt, 1.5 h, 67%.

Miyamoto et al.[10] Conversion of the 2-chloro of **8** to an amino group was accomplished by either of the two methods. The first method involved the displacement of the chloro group with sodium azide to give azide **9** followed by reduction to the amine using hexamethyldisilathiane in methanol[11] to give the amine intermediate **10** in 86% yield.

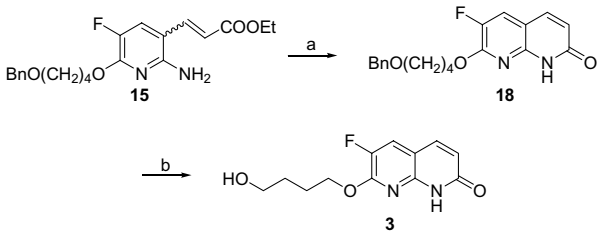
In Scheme 2, an alternate introduction of the C2-amine started with the more reactive intermediate 2,5,6-trifluoropyridin-3-carbonitrile (**11**, source: ABCR F07832MF). Addition of the alkoxide of **7** at low temperature proceeded with high selectivity at C6 to give **12**. Subsequent addition of *p*-methoxybenzylamine in a one-pot sequence resulted in the displacement of the fluoro group at the activated C2 site to give the desired product **13** in 70% yield. The *p*-methoxybenzyl group was removed using TFA to give **10** in 67% yield.

Scheme 3 continues with the reduction of the nitrile in compound **10** to aldehyde **14** with DIBAL-H. Wittig reaction of aldehyde **14** with (carbethoxymethylene)-triphenylphosphorane provided **15** as a mixture of cis and trans isomers. The mixture was hydrogenated in the presence of Raney nickel to give **16** which was easily cyclized under acidic conditions to give dihydronaphthyridinone **17**. A more rigorous hydrogenation removed the benzyl protecting group to give **2**.

In Scheme 4, the analogous 3,4-dehydro compound **3** was prepared from the common intermediate **15**. Treatment of **15** with 3 N HCl in refluxing dioxane resulted in cyclization to provide **18** in 50% yield. Conditions were selected for the hydrogenation to affect selective removal of the benzyl protecting group without reducing the naphthyridinone ring system to give **3**.



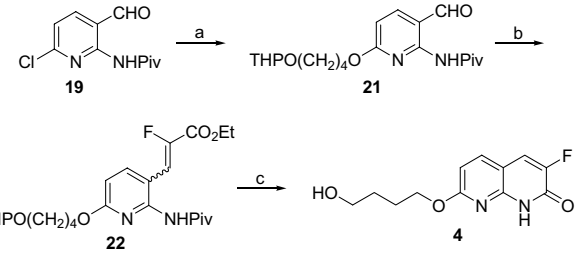
Scheme 3. Reagents and conditions: (a) DIBAL-H, THF, 0 °C, 10 min, 66–79%; (b) $Ph_3P{=}CHCO_2Et$, THF, reflux, 50%; (c) H_2 (40 psi), RaNi, THF, rt, 1 h; (d) *p*-toluenesulfonic acid, *i*-PrOH, 80 °C, 30 min, 92% over two steps; (e) H_2 (60 psi), Pd–C, EtOH, rt, 1 h, 88%.



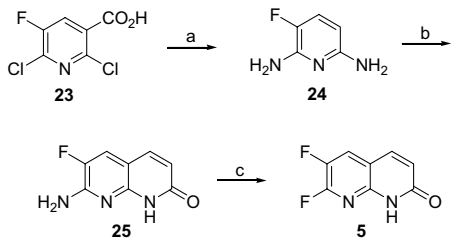
Scheme 4. Reagents and conditions: (a) 3 N HCl, dioxane, reflux, 1 h, 53%; (b) H_2 (50 psi), Pd–C, EtOH, rt, 2 h, 87%.

The synthesis of the 3-fluoro substituted naphthyridinone **4** started from the pivaloyl protected intermediate **19** (Scheme 5).[12] Similar to the preparation of **8**, reaction of the alkoxide of 4-(tetrahydro-2H-pyran-2-yloxy)-butan-1-ol[13] (**20**) with **19** gave **21** in 46% yield. With the aldehyde already in place, a Wittig reaction with triethyl-2-fluoro-2-phosphonoacetate was performed to give a cis/trans mixture of **22**. Unpurified **22** was cyclized under acidic conditions which also resulted in the removal of the THP protecting group to yield **4**.

As we wished to avoid additional synthetic and deprotection steps in the synthesis of compounds containing the 1,8-naphthyridin-2(1*H*)-one core, we prepared 6,7-difluoro-1,8-naphthyridin-2(1*H*)-one (**5**) to serve as a more general synthetic intermediate (Scheme 6). Previously in the literature, 2,5,6-trichloronicotinic acid was



Scheme 5. Reagents and conditions: (a) $THPO(CH_2)_4OH$ (**20**), NaH, DMF, 0 °C, 1.5 h, 46%; (b) 2 equiv $(EtO)_2P(O)CHFCO_2Et$, 2 equiv LiCl, 2 equiv DBU, CH_3CN, rt; (c) 3 N HCl, dioxane, reflux, 2 h, 26% over two steps.



Scheme 6. Reagents and conditions: (a) 28% NH_4OH, 150 °C (pressure vessel), 24 h, 43%; (b) D,L-malic acid, concd H_2SO_4, 115 °C, 1 h, 97%; (c) 70% HF-pyridine, KNO_2, 20 °C, 2 h, 43%.

decarboxylated during reaction with aqueous ammonia to give 3-chloro-2,6-diamino-pyridine.[14] By analogy, 2,6-dichloro-5-fluoro-nicotinic acid (**23**) upon heating with ammonia gave 2,6-diamino-3-fluoropyridine (**24**). Treatment of **24** with D,L-malic acid in concentrated sulfuric acid afforded 7-amino-6-fluoro-1,8-naphthyridin-2-one (**25**) in high yield similar to that reported in the literature for the conversion of 2,6-diaminopyridine to 7-amino-1,8-naphthyridin-2-one.[15] Finally, diazotization of **25** in the presence of HF-pyridine gave the desired 6,7-difluoro-1,8-naphthyridin-2-one (**5**).[16] Compound **5** bears an activated fluorine at the 7 position which is easily displaced by amines or alkoxides and thus, provides a useful intermediate for further investigation of the 6-fluoro-1,8-naphthyridin-2-one series.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2007.09.090.

References and notes

1. (a) Bouzard, D.; Di Cesare, P.; Essiz, M.; Jacquet, J. P.; Ledoussal, B.; Remuzon, P.; Kessler, R. E.; Fung-Tomc, J. *J. Med. Chem.* **1992**, *35*, 518–525; (b) Breault, G.; Eyermann, C. J.; Geng, B.; Morningstar, M.; Reck, F. PCT Int. Appl. WO2006134378, **2006**; (c) Matsumoto, J.; Takase, Y.; Nishimura, Y. U.S. Patent Appl. US 4,359,478, **1982**.
2. Leonard, J. T.; Gangadhar, R.; Gnanasam, S. K.; Ramachandran, S.; Saravanan, M.; Sridhar, S. K. *Biol. Pharm. Bull.* **2002**, *25*, 798–802.
3. (a) Ferrarini, P. L.; Mori, C.; Badawneh, M.; Calderone, V.; Calzolari, L.; Loffredo, T.; Martinotti, E.; Saccomanni, G. *Eur. J. Med. Chem.* **1998**, *33*, 383–397; (b) Matsuura, A.; Ashizawa, N.; Hase, T. PCT Int. Appl. WO9412499, **1994**.
4. Ban, H.; Muraoka, M.; Morisita, K.; Ohashi, N. *Heterocycles* **2005**, *65*, 2763–2770.
5. (a) Booth, R. F. G.; Manley, P. W.; Buckham, S. P.; Hassall, D. G.; Honey, A. C.; Lad, N.; Lunt, D. O.; Oswald, S.; Porter, R. A.; Tuffin, D. P. *Platelets* **1992**, *3*, 129–136; (b) Ferrarini, P. L.; Mori, C.; Miceli, M.; Franconi, F. *Eur. J. Med. Chem.* **1994**, *29*, 735–741.
6. (a) Aotsuka, T.; Kumazawa, K.; Wagatsuma, N.; Ishitani, K.; Nose, T. PCT Int. Appl. WO2001042244, **2001**; (b) Takayama, K.; Iwata, M.; Hisamichi, H.; Okamoto, Y.; Aoki, M.; Niwa, A. *Chem. Pharm. Bull.* **2002**, *50*, 1050–1059.
7. (a) Boehm, J. C.; Callahan, J. F.; Hall, R. F.; Lin, X. Widdowson, K. L. PCT Int. Appl. WO2004073628, **2004**; (b) Adams, N. D.; Darcy, M. G.; Dhanak, D.; Duffy, K. J.; Fitch, D. M.; Knight, S. D.; Newlander, K. A.; Shaw, A. N. PCT Int. Appl. WO2006113432, **2006**.
8. (a) Clark, J. D.; Davis, J. M.; Favor, D.; Fay, L. K.; Franklin, L.; Henegar, K. E.; Johnson, D. S.; Nichelson, B. J.; Ou, L.; Repine, J. T.; Walters, M. A.; White, A. D.; Zhu, Z. U.S. Patent Appl. US 2005043309, **2005**; (b) Johnson, D. S.; Singer, J. M.; White, A. D. PCT Int. Appl. WO2006090273, **2006**; (c) Favor, D. A.; Johnson, D. S.; Repine, J. T.; White, A. D. PCT Int. Appl. WO2006090272, **2006**.
9. (a) Ismail, F. M. D. *J. Fluorine Chem.* **2002**, *118*, 27–33; (b) Park, B. K.; Kitteringham, N. R.; O'Neill, P. M. *Ann. Rev. Pharmacol. Toxicol.* **2001**, *41*, 443–470; (c) Razgulin, A. V.; Mecozzi, S. *J. Med. Chem.* **2006**, *49*, 7902–7906.
10. Miyamoto, T.; Egawa, H.; Shibamori, K.; Matsumoto, J. *J. Heterocycl. Chem.* **1987**, *24*, 1333–1339.
11. Capperucci, A.; Degl'Innocenti, A.; Funicello, M.; Mauriello, G.; Scafato, P.; Spagnolo, P. *J. Org. Chem.* **1995**, *60*, 2254–2256.
12. Turner, J. A. *J. Org. Chem.* **1990**, *55*, 4744–4750.
13. Petroski, R. J. *Synth. Commun.* **2003**, *33*, 3251–3259.
14. (a) Mutterer, Francis; Weis, C. D. *Helv. Chim. Acta* **1976**, *59*, 222–229; (b) Laeckmann, D.; Rogister, F.; Dejardin, J. V.; Prosperi-Meys, C.; Geczy, J.; Delarge, J.; Masereel, B. *Bioorg. Med. Chem.* **2002**, *10*, 1793–1804.
15. Carboni, S.; De Settimo, A.; Pirisino, G. *Ann. Chim.* **1964**, *54*, 883–890.
16. *Experimental procedure for the synthesis of* **5**: A mixture of 2,6-dichloro-5-fluoronicotinic acid (**23**) (140 g, 670 mmol, Alfa Aesar) in NH_4OH (1.2 L, 28–30%, Caledon) was heated to 150 °C in a commercial grade stainless steel pressure vessel (2 L volume) for 24 h, cooled to room temperature, and diluted with EtOAc (2 L). The mixture was washed with brine, dried over sodium sulfate, and concentrated to give 3-fluoropyridine-2,6-diamine (**24**) as a dark solid (36.5 g, 287 mmol, 43%). ^{1}H NMR (400 MHz, δ ppm): 7.03 (dd, 1H), 5.85 (dd, 1H), 4.34 (br s, 2H), 4.07 (br s, 2H).
D,L-Malic acid (112.7 g, 842 mmol, Alfa Aesar) was added to a solution of **24** (40 g, 314 mmol) in concd H_2SO_4 (154 mL, Caledon). The mixture was heated to 115 °C for 1 h. Adequate ventilation should be maintained to avoid inhalation of the carbon monoxide by-product of this reaction. The mixture was cooled to room temperature, ice was added, and the pH was adjusted to ~7 by adding NH_4OH (28–30%, Caledon) to give a precipitate, which was filtered and dried at 40 °C to afford 7-amino-6-fluoro-1,8-naphthyridin-2(1*H*)-one (**25**) as a yellow solid (55 g, 307 mmol, 97%). ^{1}H NMR (400 MHz, δ ppm): 11.65 (s, 1H), 7.62 (M, 2H), 7.07 (br s, 2H), 6.15 (d, 1H).
HF-pyridine complex (187 mL, containing 70% HF, Alfa Aesar) was added to **25** (64.2 g, 358 mmol) at ~5 °C. After **25** dissolved, KNO_2 (42.6 g, 501.2 mmol, Alfa Aesar) was added in portions at 20 °C. The mixture was stirred continuously for 2 h at 20 °C (yellow solid formed) and put into ice to give a solid. The solid was collected and then washed with ether to give the desired compound as the hydrofluoride salt. This solid was suspended in water again, adjusted to pH ~8 by the addition of sat. $NaHCO_3$, filtered, washed with water followed by ether, and dried at 40 °C to give 6,7-difluoro-1,8-naphthyridin-2(1*H*)-one (**5**) as a yellow solid (28 g, 153 mmol, 43%). ^{1}H NMR (400 MHz, δ ppm): 12.39 (s, 1H), 8.35 (dd, 1H), 7.90 (d, 1H), 6.18 (d, 1H).