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Synthesis of α,α-Difluoroethyl Aryl and Heteroaryl Ethers

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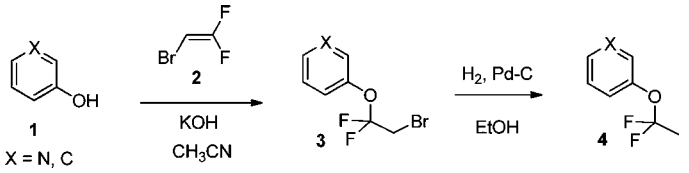
ABSTRACT



Fluorine plays a critical role in modern medicinal chemistry due to its unique properties, and new methods for its incorporation into target molecules are of high interest. An efficient new method for the preparation of aryl-α,α-difluoroethyl ethers (4) via addition of aryl and heteroaryl alcohols (1) to commercially available 2-bromo-1,1-difluoroethene (2) and subsequent hydrogenolysis is presented. This procedure is an attractive alternative to existing methods that employ harshly reactive fluorinating systems such as xenon difluoride and hydrogen fluoride.

Fluorine plays a critical role in modern medicinal chemistry due to its unique stereoelectronic properties and small size.[1,2] Electron-rich aromatic rings that are prone to oxidation by metabolic enzymes can be stabilized through the judicious incorporation of electron-withdrawing fluorine, and the high C−F bond energy makes fluorine an attractive isostere for the replacement of hydrogen atoms at specific metabolic soft spots including Ar−H and hydrogen atoms α to heteroatoms (i.e., $-CH_2OR$).[3] Additionally, fluorine has been used as an isostere for ethyl/isopropyl (CF_3), carbonyl (CF_2), hydroxyl (CF, CF_2, CF_2H), and amide functionalities[4−7] and can impart unique structural effects relative to the parent hydrocarbon chain thereby enabling access to alternative conformational space.[8,9] Fluorine-induced changes in lipophilicity and pK_a can improve target binding, bioavailability, and/or CNS exposure by reducing interaction with various cytochrome P450s and efflux proteins.[3] Approximately 30% of the 30 top selling small molecule drugs in recent years contain fluorine, often as direct aryl substituents (e.g., Lipitor, Crestor, Celebrex, Prozac) but also as aliphatic fluorine (e.g., Prevacid, Protonix).[10] Thus, the utility of fluorine as a means to impart desirable properties to drug molecules has fostered intense research on new methods

(1) Hagmann, W. K. *J. Med. Chem.* **2008**, *51*, 4359–4369.
(2) Kirk, K. L. *J. Fluorine Chem.* **2006**, *127*, 1013–1029.
(3) Park, K. P.; Kitteringham, N. R.; O'Neill, P. M. *Annu. Rev. Pharmacol. Toxicol.* **2001**, *41*, 443–470.
(4) Kozikowski, A. P.; Wu, J. P. *Tetrahedron Lett.* **1990**, *31*, 4309–12.
(5) Palmer, J. T.; Bryant, C.; Wang, D.-X.; Davis, D. E.; Setti, E. L.; Rydzewski, R. M.; Venkatraman, S.; Tian, Z.-Q.; Burrill, L. C.; Mendonca, R. V.; Springman, E.; McCarter, J.; Chung, T.; Cheung, H.; Janc, J. W.; McGrath, M.; Somoza, J. R.; Enriquez, P.; Yu, Z. W.; Strickley, R. M.; Liu, L.; Venuti, M. C.; Percival, M. D.; Falgueyret, J.-P.; Prasit, P.; Oballa, R.; Riendeau, D.; Young, R. N.; Wesolowski, G.; Rodan, S. B.; Johnson, C.; Kimmel, D. B.; Rodan, G. *J. Med. Chem.* **2005**, *48*, 7520–7534.
(6) Black, W. C.; Bayly, C. I.; Davis, D. E.; Desmarais, S.; Falgueyret, J.-P.; Leger, S.; Li, C. S.; Masse, F.; McKay, D. J.; Palmer, J. T.; Percival, M. D.; Robichaud, J.; Tsou, N.; Zamboni, R. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 4741–4744.
(7) Garrett, G. S.; Emge, T. J.; Lee, S. C.; Fischer, E. M.; Dyehouse, K.; McIver, J. M. *J. Org. Chem.* **1991**, *56*, 4823–6.
(8) Müller, K.; Faeh, C.; Diederich, F. *Science* **2007**, *317*, 1881–1886.
(9) Horne, D. B.; Bartberger, M. D.; Kaller, M. R.; Monenschein, H.; Zhong, W.; Hitchcock, S. A. *Tetrahedron Lett.* **2009**, *50*, 5452–5455.
(10) O'Hagan, D. *J. Fluorine Chem.* **2010**, *131*, 1071.
(11) Hiyama, T. *Organofluorine compounds: chemistry and applications*; Springer: Berlin, Heidelberg, and New York, 2000.
(12) Tomashenko, O. A.; Grushin, V. V. *Chem. Rev. (Washington, DC, U.S.)* **2011**, *111*, 4475–4521.
(13) Furuya, T.; Klein, J. E. M. N.; Ritter, T. *Synthesis* **2010**, 1804–1821.
(14) Furuya, T.; Kuttruff, C. A.; Ritter, T. *Curr. Opin. Drug Discovery Dev.* **2008**, *11*, 803–819.
(15) Lee, E.; Kamlet, A. S.; Powers, D. C.; Neumann, C. N.; Boursalian, G. B.; Furuya, T.; Choi, D. C.; Hooker, J. M.; Ritter, T. *Science (Washington, DC, U.S.)* **2011**, *334*, 639–642.
(16) Cho, E. J.; Senecal, T. D.; Kinzel, T.; Zhang, Y.; Watson, D. A.; Buchwald, S. L. *Science (Washington, DC, U.S.)* **2012**, *328*, 1679–1681.
(17) Nagib, D. A.; MacMillan, D. W. C. *Nature (London, U.K.)* **2011**, *480*, 224–228.
(18) Zhao, Y.; Gao, B.; Hu, J. *J. Am. Chem. Soc.* **2012**, *134*, 5790–5793.

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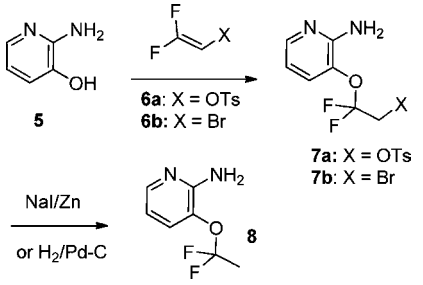
and reagents for its incorporation.[1,11–20] As stated by G. K. Surya Prakash, "Fluorine has become a driving force – it's the new kingpin of drug discovery."[21]

Our contribution to this area originated from a desire for an efficient, scaleable, and environmentally safe way to replace an aryl ethoxy group with the α,α-difluoroethoxy group to reduce the extent of oxidative metabolism α to oxygen. Xenon difluoride (XeF_2) is an established reagent for the incorporation of this group by skeletal rearrangement of aryl or heteroaryl carbonyls, but the conversion involves excessive use of corrosive XeF_2/HF and, especially with acetophenone substrates, suffers from low yields.[9,22–24] Limited commercial availability of aryl aldehydes and acetophenones also limits wide application of this procedure. Other methods include conversion of thionoesters into α,α-difluoroethers via the action of nucleophilic fluorine sources such as DAST,[25] BrF_3,[26] or nBu$_4$NH$_2$F$_3$.[27] Drawbacks to these methods include employment of toxic and corrosive fluorinating agents. Herein we report an alternative method for the introduction of the α,α-difluoroethoxy group that begins with the addition of aryl or heteroaryl alcohols to commercially available 2-bromo-1,1-difluorobromoethene. The resultant difluorobromoethyl group can be dehalogenated to cleave the bromine atom, or conversely the bromine can be used as a functional handle for further structural transformation (Scheme 1).

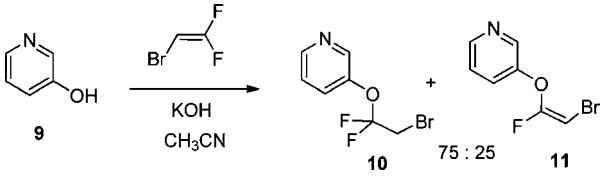
In developing this method we considered a report by Fang et al. whereby oxygen nucleophiles are added to 2,2-difluorovinyl tosylate **6a** to yield 1,1-difluoro-2-tosyl aryl ethers such as **7a**.[28] In contrast to established methods, this strategy would allow us to purchase the carbon–fluorine bond rather than install it with reactive fluorinating reagents. We reasoned that an attractive route to the α,α-difluoroethoxy group could entail subsequent reductive cleavage of the tosylate.[29] Our pilot studies centered on the addition of commercially available 2-aminopyridin-3-ol (**5**) to the vinyltosylate **6a** to yield **7a**, followed by zinc/NaI mediated reductive cleavage of the C–OTs bond to give the target ether **8** (Scheme 1). Deficiencies in the strategy were soon apparent: requisite S_N2 displacement of –OTs with NaI was extremely sluggish, and the in situ reduction required large amounts of zinc which would complicate scaleup. We then considered that an alternative source of electrophilic difluoroethene, commercial 2-bromo-1,1-difluoroethene (**6b**), would obviate the OTs/halide conversion and provide a route to **8** via hydrogenolysis (Scheme 1).

Scheme 1. Synthetic Strategy



In practice treatment of **5** with **6b** and KOH in acetonitrile produced the desired ether **7b** in 84% yield, and subsequent hydrodehalogenation provided the target **8** in 82% yield. In determining the generality of this method we repeated the reaction conditions with simple 3-hydroxypyridine **9**: treatment with **6b** and KOH in acetonitrile at room temperature gave the desired product **10**, but in this case it also gave ~25% of the elimination product **11** (Table 1).[30] This side product was not observed with the –OTs reagent.[28] Replacement of KOH with a stronger or weaker base (KOtBu/K_2CO_3) did not change the product ratio, but the weaker base resulted in a much slower reaction (~24 h vs 2 h). The elimination result can be explained mechanistically, as the anionic aryloxide intermediate from **9** is poised to eliminate fluoride, whereas this process is suppressed in the case of **5** due to the internal proton donor (NH_2). Given these results, we conducted the reaction in the presence of water as a green proton source (Table 1). While small amounts of water gave a slower reaction, the extent of elimination was drastically reduced (entry 1 vs 2). In subsequent experiments we compensated

Table 1. Base and Solvent Effects

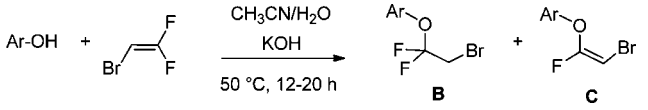


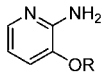
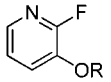
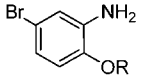
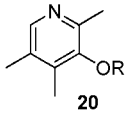
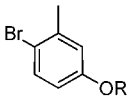
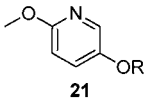
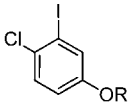
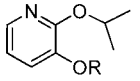
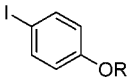
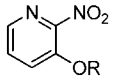
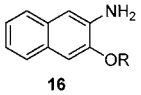
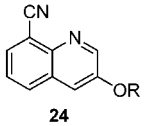
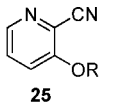
entry	water	t (°C)	time (h)	**10:11**[a]	yield[a]
(1)	–	rt	2	76:24	71%
(2)	5%	rt	36	97:3	53%
(3)	2.5%	50	5	93:7	74%
(4)	5%	50	10	96:4	82%

[a] Product ratio determined by ^{1}H NMR; yield reported is combined yield after chromatography.

(19) Fujiwara, Y.; Dixon, J. A.; Rodriguez, R. A.; Baxter, R. D.; Dixon, D. D.; Collins, M. R.; Blackmond, D. G.; Baran, P. S. *J. Am. Chem. Soc.* **2012**, *134*, 1494–1497.
(20) Prakash, G. K. S.; Ledneczki, I.; Chacko, S.; Olah, G. A. *Org. Lett.* **2008**, *10*, 557–560.
(21) Ritter, S. K. *Chem. Eng. News* **2012**, *90*, 10–17.
(22) Zajc, B.; Zupan, M. *J. Org. Chem.* **1990**, *55*, 1099–102.
(23) Stavber, S.; Koren, Z.; Zupan, M. *Synlett* **1994**, 265–6.
(24) Tamura, M.; Matsukawa, Y.; Quan, H.-d.; Mizukado, J.; Sekiya, A. *J. Fluorine Chem.* **2004**, *125*, 705–709.
(25) Bunnelle, W. H.; McKinnis, B. R.; Narayanan, B. A. *J. Org. Chem.* **1990**, *55*, 768–770.
(26) Rozen, S.; Mishani, E. *J. Chem. Soc., Chem. Commun.* **1993**, 1761–1762.
(27) Kuroboshi, M.; Hiyama, T. *Synlett* **1994**, 251–252.
(28) Fang, X.; Wu, Y.-M.; Deng, J.; Wang, S.-W. *J. Fluor. Chem.* **2004**, *125*, 1481.
(29) Fujimoto, Y.; Tatsuno, T. *Tetrahedron Lett.* **1976**, 3325–6.

Table 2. Reaction Scope



entry	B ($R=CF_2CH_2Br$)	B:C ratio	yield (%)	entry	B ($R=CF_2CH_2Br$)	B:C ratio	yield (%)[a]
(1)	 **7b**	**>95 : 5**	**84%**	(9)	 **19**	**>95:5**	**87%**
(2)	 **12**	**>95 : 5**	**94%**	(10)	 **20**	**>95:5**	**92%**
(3)	 **13**	**95 : 5**	**93%**	(11)	 **21**	**95 : 5**	**91%**
(4)	 **14**	**95 : 5**	**95%**	(12)	 **22**	**86 : 14**	**95%**
(5)	 **15**	**95 : 5**	**97%**	(13)	 **23**	**>95:5**	**64%**
(6)	 **16**	**>95:5**	**97%**	(14)	 **24**	**95:5**	**45%**
(7)	 **17**	**>95:5**	**97%**	(15)	 **25**	**>95:5**	**66%**
(8)	 **18**	**95 : 5**	**88%**	(16)[b]	**25**	**>95:5**	**90%**

[a] Combined yield after silica gel chromatography. [b] KOH was replaced by K_2CO_3, and the reaction duration was extended to 30 h.

for the reduced reaction rate by raising the reaction temperature to 50 °C (entry 2 vs 3 and 4), and the optimized conditions provided a 96:4 ratio of **10** and **11** in a combined yield of 82% (entry 4).

These optimal conditions were applied to a variety of aryl and heteroaryl rings and, in general, gave good-to-excellent yields (84−97%) with $<5\%$ elimination (Table 2).[31] We attribute the poorer product ratio of entry 12 to steric effects imparted by the isopropoxy group in **22** that hinder proton transfer, and lower yields in select cases to reduced nucleophilicity of the aryloxide (entry 13) or to competing nitrile hydrolysis by KOH (entries 14, 15). In the latter case, better product yields were obtained with K_2CO_3, which required an extended reaction time but gave a much improved yield (entry 16).

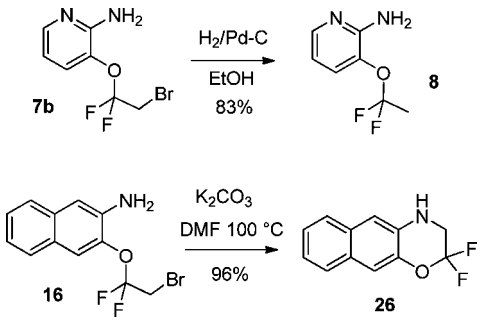
(30) The structure of **11** was determined by NMR and MS.

(31) In a typical reaction, a stock solution was prepared by bubbling 1,1-difluorobromoethene gas via a cannula into an ice cold tarred flask of acetonitrile to achieve a concentration of ~1 M. In a second flask containing 3.0 mmol of the aryl alcohol in acetonitrile was added 9.3 mmol of KOH followed by 3.0 mmol of 1,1-difluorobromoethene transferred via syringe from the stock solution. The resultant mixture was heated to 50 °C for 12 h. On completion as assessed by TLC and LCMS, the mixture was cooled, passed through a plug of silica gel, and concentrated to yield the product mixture.

(32) Bordwell, F. G.; Brannen, W. T., Jr. *J. Am. Chem. Soc.* **1964**, *86*, 4645–4650.

A few simple transformations further demonstrate the utility of this method (Scheme 2). In the first example, hydrogenation of bromodifluoro ether **7b** provided the α,α-difluoroethyl ether **8** in 83% yield. Consistent with the literature report,[28] we have found that these *aryl*/*heteroaryl* α,α-difluoroethyl ether products are stable to aqueous workup and silica chromatography and thus may constitute reasonable pharmaceutical targets. In fact, our attempts to hydrolyze these compounds under forcing conditions (aqueous NaOH or HCl, 70 °C) further demonstrated the resistance of this functionality to hydrolysis. In contrast, *alkyl* α,α-difluoroethyl ethers are reportedly quite susceptible to hydrolysis and must be handled carefully.[25−27]

Scheme 2



In another demonstration of the utility of this method, intramolecular displacement by an *ortho*-amine group provides a route to fused morpholines such as **26**. However, other attempts to displace the bromine atom of **16** intermolecularly with pyrrolidine (DMF, 120 °C) failed, yielding only starting material and suggesting impediment of an intermolecular S_N2 attack by the geminal adjacent fluorine atoms.[32]

In conclusion we have described a new method for the incorporation of the α,α-difluorobromoethoxy group into aryl and heteroaryl systems in high yield. Competing elimination of fluoride to yield the 1-fluoro-2-bromo vinyl ether can be reduced by introducing water as a proton source. The product 2-bromo-1,1-difluoroethyl ether can be further manipulated by hydrogenolysis of bromine to provide ready access to the α,α-difluoroethyl ethers, or alternatively, intramolecular displacement of the bromine atom by an internal nucleophile can provide access to fused morpholines. This method should prove useful as an additional tool for the incorporation of fluorine in pharmaceutical and agrochemical applications.

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Supporting Information Available. Experimental procedures and spectroscopic data for all new compounds, including fluorine NMR spectra for representative structures. This material is available free of charge via the Internet at http://pubs.acs.org.

The authors declare no competing financial interest.