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Synthesis and conformational analysis of α,α-difluoroalkyl heteroaryl ethers

Daniel B. Horne *, Michael D. Bartberger *, Matthew R. Kaller, Holger Monenschein, Wenge Zhong, Stephen A. Hitchcock

Departments of Medicinal Chemistry and Molecular Structure and Design, Amgen, Inc., One Amgen Center Drive, Thousand Oaks, CA 91320-1799, USA

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ABSTRACT

We report the efficient synthesis of difluoroalkyl aryl ethers from the rearrangement of heteroaryl ketones and aldehydes, mediated by xenon difluoride and HF/pyridine in methylene chloride at room temperature. Computational analysis of difluoroalkylethers shows that there is potential to allow access to conformational space not accessible to the hydrogenated parent.

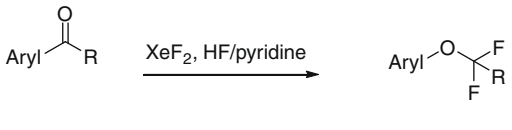
The increasing use of fluorine atoms as compact lipophilic and metabolic stabilizing groups in potential drug candidates[1] has stimulated the interest in the development of new reactions and reagents to introduce fluorine into molecules.[2] During the course of the synthesis of several aryl ether-containing lead compounds for a drug discovery project, it was postulated that a heteroaryl core compound containing a α,α-difluoroalkylether group might confer additional potency, stability, and improved efficacy compared to its alkyl ether analogs. XeF_2,[3] a relatively mild electrophilic fluorinating reagent, has been used in organic synthesis for fluorodecarboxylation[4] as well as electrophilic fluorination of hydrocarbons,[5] aromatic compounds,[6] and alkenes.[7] The XeF_2-mediated rearrangement of arylketones and aldehydes to α,α-difluoroalkylethers has also been described (Fig. 1).[8] However, the rearrangement with heteroaryl carbonyls, leading to products typically used in drug discovery, has not been published. In addition, many acetophenone substrates suffered from poor reactivity and low yields due to competitive electrophilic aromatic ring fluorination. We postulated that the lower nucleophilicity of some heteroaryl ketones might preclude the undesirable aromatic ring fluorination and lead to a more efficient and general method to prepare heterocyclic difluoroethers.

We began our initial efforts centered on the rearrangement of 3-acetylquinoline to 3-(1,1-difluoroethoxy)quinoline and screening reaction conditions to obtain optimal yields (Table 1).[9] Our initial screening conditions, 1.0 equiv of XeF_2 with 5.0 equiv of HF in pyridine resulted in only 5% conversion to product (entry 1). Additional HF (30 equiv) facilitated the reaction and increased the conversion to 90%, resulting in 75% isolated yield (entry 2). Increasing the quantity of XeF_2 to 2.0 equiv with 30 equiv of HF forced the reaction to completion and resulted in 87% isolated yield (entry 3). A limited solvent screen showed no improvement over CH_2Cl_2 (entries 5 and 6) and in the case of neat 70 wt % HF in pyridine resulted in degradation of the product (entry 7).

Variation of the alkyl group showed the reaction is tolerant to a variety of simple alkyl groups and that an aldehyde also gives the rearranged product in good yield (Table 2). However, the reaction appears to be somewhat limited by sterics as the reaction with the *i*-Pr substituent failed to give complete conversion resulting in moderate yield (entry 4) and in the reaction with a bulky *t*-butyl group <5% conversion was observed (entry 5). The more electron-rich phenyl ring migrated preferentially over the quinoline ring to give a single regioisomer (entry 6), but a poor yield resulted due to concomitant formation of a byproduct resulting from aromatic ring fluorination at the *para* position of the electron-rich phenoxy group.

Next, a range of aryl and heteroaryl ketones were subjected to the optimized rearrangement conditions and in most cases gave good yields of the desired products (Table 3). Of the substrates run in this reaction, four substrates failed to give the desired products (entries 9–12). First, the indole and *N*-methylindole did not participate in the reaction and resulted in low conversion to product (entries 9 and 10). Also, acetylpyrazine was not tolerated in the reaction, and only degradation products were observed (entry 11). Finally, the trifluoromethylketone failed to react and led only to recovered starting material (entry 12).

Since our original interest in the α,α-difluoroalkylether group came from a medicinal chemistry project where attempts to gain potency with alkoxyether groups appended to the inhibitor were



1 2

Figure 1. Xenon difluoride arylketone rearrangement.

* Corresponding authors. Tel.: +1 805 323 5250; fax: +1 850 480 3016 (D.B.H.).
E-mail addresses: dhorne@amgen.com (D.B. Horne), mbartber@amgen.com (M.D. Bartberger).

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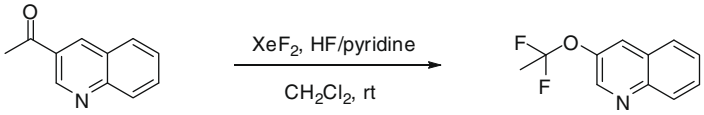
Table 1
Optimization of 3-acetylquinoline rearrangement



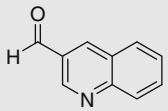
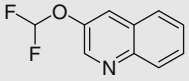
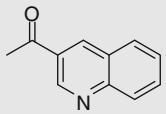
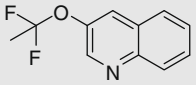
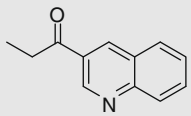
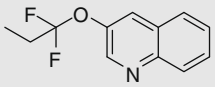
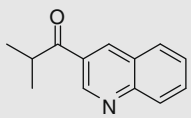
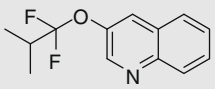
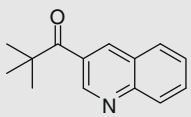
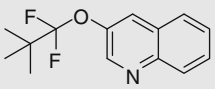
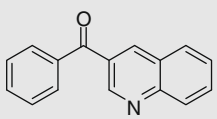
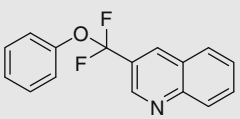
Entry	XeF_2 (equiv)	HF (equiv)	Solvent	Temp, time	Conversion (%)	Yield (%)
1	1.0	5.0	CH_2Cl_2	23 °C, 22 h	5	—
2	1.0	30.0	CH_2Cl_2	23 °C, 22 h	90	75
3	2.0	30.0	CH_2Cl_2	23 °C, 22 h	100	87
4	1.0	—	CH_2Cl_2	23 °C, 22 h	No Rxn	—
5	2.0	30.0	$CHCl_3$	23 °C, 22 h	100	85
6	2.0	30.0	CCl_4	23 °C, 22 h	100	71
7	2.0	220.0	—	23 °C, 22 h	100	15

unsuccessful. We proposed, based upon literature observations,[10,11] that the lipophilic portion of our substrate molecule, which was accessible and led to increased potency with alkyl groups, might also be accessed by the special structural features inherent in the α,α-difluoroalkylether group. These observations were born out both in the computational analysis described below and in observed increases in potency between alkylether and fluorinated analogs in in vitro enzyme assays.

Fluorination of aryl ethers on the alkyl chain adjacent to oxygen imparts significant changes to the accessible and preferred conformations of the tether,[7] potentially allowing for access to conformational space not accessible to the hydrogenated parent. Large basis quantum mechanical calculations and several experimental studies[8] have demonstrated that while methoxybenzene adopts a planar conformation ($\varphi C_{ortho}–C_{ipso}–O–C_{alkyl} = 0°$), the $–OCF_3$ group of trifluoromethoxybenzene adopts an orientation perpendicular to the plane of the aryl ring.

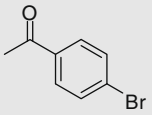
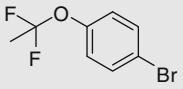
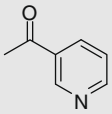
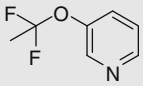
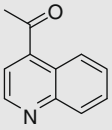
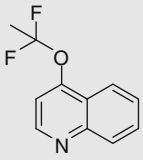
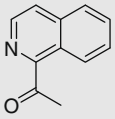
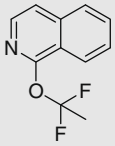
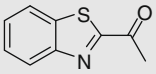
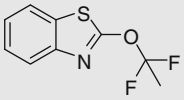
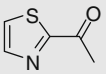
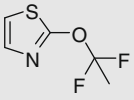
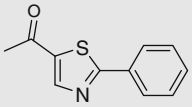
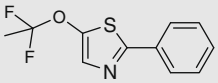
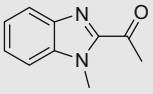
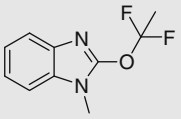
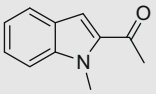
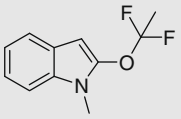
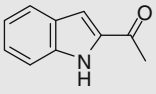
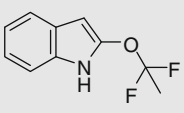
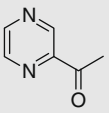
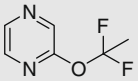
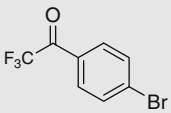
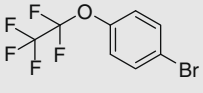
Figure 2 depicts the B3LYP/6-31G* torsional potential for α,α-difluoroaryl system **2** of Table 2, along with its dihydro analog. It is predicted that for quinoline-derived species **2**, although α,α-difluorination does not fully give rise to a preference for the perpendicular conformation, the energy difference between the planar ($\varphi = 0°$) global minimum energy structure and the near-perpendicular ($\varphi = 75.3°$) local minimum[12] in **2** is reduced to only 0.5 kcal/

Table 2
Substitution of alkyl group in rearrangement

Entry	ArC=OR	Product	Yield (%)
1			74
2			87
3			68
4[a]			39
5			<5% conversion
6			53

[a] Reaction only proceeded to 52% conversion.

Table 3
Aryl and heteroaryl ketones

Entry	ArC=OR	Product	Yield (%)
1			53
2			56
3			90
4[a]			73
5			76
6			54
7			82
8			70
9			0
10			Trace
11			0
12			0

[a] Reaction was run with 4.0 equiv XeF_2 and 60 equiv HF.

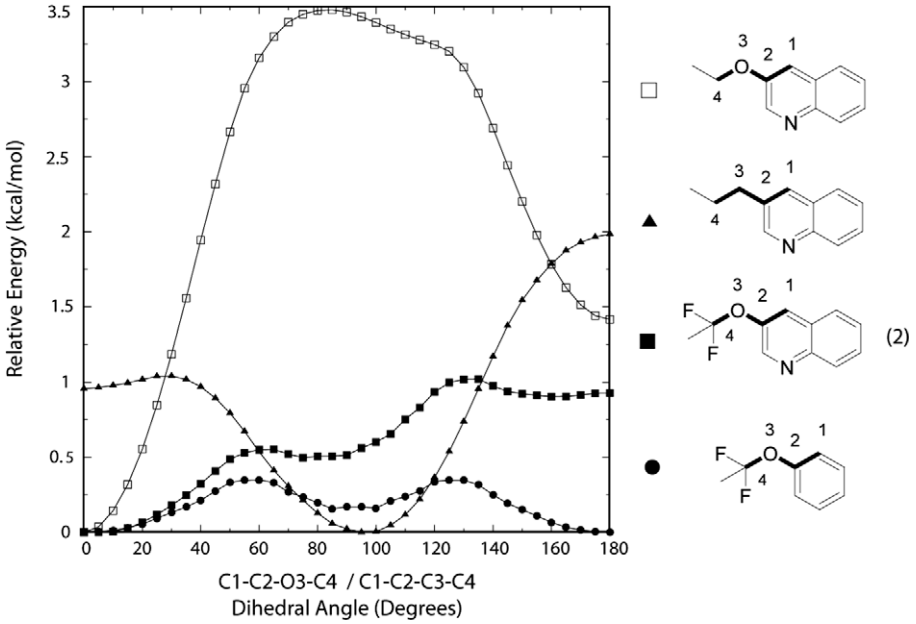


Figure 2. Dihedral angle plot (B3LYP/6-31G*) for difluoro-, dihydroethoxy-, and *n*-propyl-substituted aryl species.

mol. This is in stark contrast to the perhydro system, the perpendicular orientation of which (a transition state for interconversion between planar minima) lies nearly 3.5 kcal/mol above the global minimum ($\varphi = 0°$). In the case of non-aza aryl ethers, such as difluoroethoxybenzene (Fig. 2), the energy difference is even less (ca. 0.2 kcal/mol) and thus the population of the near-perpendicular local minimum conformation further increases. Electron withdrawal resulting from successive fluorination reduces the availability and conjugation of oxygen lone pairs into the arene pi system. The 0.2 kcal/mol versus 0.5 kcal/mol difference in energy between the near-perpendicular and planar conformations of phenyl-derived versus quinoline-derived aryl ethers can be attributed to the competing electron-withdrawing effect of the ring nitrogen in the latter, facilitating some degree of additional conjugation with the ring. Thus, α-fluorination of aryl ethers allows access to conformational space both coplanar and perpendicular to the plane of the ring. This is in contrast to the non-fluorinated analogs, where the alkyl or alkoxy substituent is more restricted to perpendicular or coplanar conformations, respectively.

In summary, we describe a general method for difluoroether formation from heteroaryl ketones or aldehydes. The reaction was shown to be compatible with a wide array of heteroaryl carbonyl compounds to allow efficient entry to 1,1-difluoroalkylethers. Given the utility of fluorination in improving metabolic stability of drug-like molecules, fluorinated aryl ethers may find utility as replacements for alkyl-substituted aromatic rings with potentially increased metabolic stability, while retaining conformational characteristics more similar to alkyl-substituted arenes than those bearing alkoxyl substituents.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2009.07.060.

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9. Warning, xenon difluoride is toxic and has a low vapor pressure. A well-ventilated fume hood should be used for all procedures using the reagent and reaction workup. General procedure: To a polyethylene vial are added the ketone substrate (0.30 mmol) and CH_2Cl_2 (1.0 mL). Xenon difluoride (0.60 mmol, 2.0 equiv) is added followed by 70% HF in pyridine (9.0 mmol, 0.25 mL, 30 equiv). The vial is sealed and stirred overnight at room temperature. The reaction mixture is diluted with CH_2Cl_2 (10 mL), and the reaction is quenched by slow addition to saturated aqueous $NaHCO_3$ (10 mL) containing excess solid $NaHCO_3$ (0.500 g). The organic layer was extracted, the aqueous layer extracted with CH_2Cl_2 (2×10 mL), the combined organic layers were dried ($MgSO_4$), and concentrated. Purification by flash chromatography gives the product.
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12. From unconstrained B3LYP/6-31G* optimization and frequency analysis (GAUSSIAN 03; Frisch et al., Gaussian, Inc., Wallingford, CT, 2004).