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COMMUNICATION

Fluorination of 2-substituted benzo[*b*]furans with Selectfluor™

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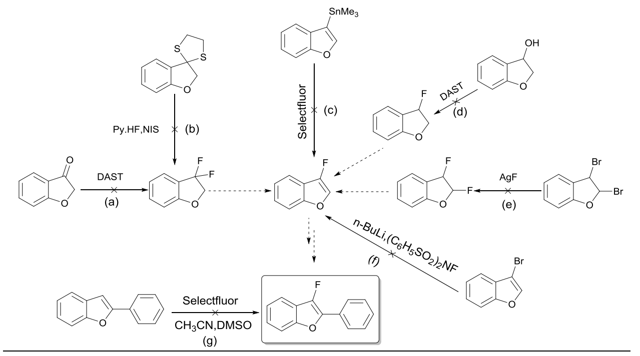
An efficient protocol was developed to access 3-fluoro-2-hydroxy-2-substituted benzo[*b*]furans with Selectfluor™ as the fluorinating reagent in MeCN and water. By utilizing $SOCl_2$/Py as the dehydration agent, the compounds above were readily converted to 3-fluorinated, 2-substituted benzo[*b*]furans in high yields.

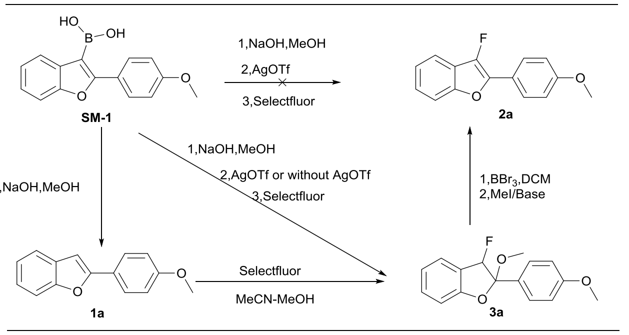
Heterocyclic structures play a vital role in pharmaceuticals and bioactive natural products. The benzo[*b*]furan ring is one of the most prevalent heterocyclic structural motifs that occur in a wide variety of isolated natural products[1] and is extremely important in medicinal chemistry.[2] 2-Arylbenzo[*b*]furans have recently attracted considerable attention due to their versatile pharmaceutical activities, such as inhibition of cholinesterase activity,[3] and their antitumour,[4] antiviral,[5] antiplasmodial,[6] antioxidant[7] and anti-HIV properties.[8] On the other hand, fluorinated compounds often exhibit remarkably different chemical, physical and pharmacological properties in comparison with their fluorine-free analogues,[9] which make them widely applicable in diverse areas ranging from pharmaceuticals to materials science.[10] The C(3)-position in 2-arylbenzo[*b*]furans is usually a metabolic soft spot in vivo. Therefore, introduction of F at this position may block drug metabolism and then improve pharmacokinetic properties[9e]. We have recently been interested in the design of C(3)-F-substituted 2-arylbenzo[*b*]furans for drug discovery and development. Literature mining revealed very few methods for the synthesis of C(3)-F-substituted benzo[*b*]furans. Herein we report an efficient protocol to generate C(3)-fluorinated benzo[*b*]furans as important building blocks for drug discovery.

Initially, various different reported methods were screened (Scheme 1): a) direct difluoro substitution of a ketone using DAST;[11] b) difluoro substitution of a thioketal with Py HF;[12] c) trialkylstannyl substitution for electrophilic fluorination;[13] d) conversion from an alcohol into a F with DAST;[14] e) Br-F exchange;[15] f) metal-induced introduction of F;[16] and, g) introduction of F by using Selectfluor in MeCN and DMSO.[17] Unfortunately, none of these methods gave the fluorinated product. In 2009, Ritter and co-workers reported an elegant approach for introducing F onto aromatic rings from boronic acids[18] through AgOTf exchange. Although a benzo[*b*]furan ring was not disclosed in the original paper, it is still interesting to explore the chemistry on this new class of substrates. Benzo[*b*]furan boronic acid **SM-1** was thus prepared according to the known procedure.[19] Surprisingly, instead of the target compound **2a**, a new product, 3-fluoro-2-methoxy-2-(4-methoxyphenyl)-2,3-dihydrobenzofuran (**3a**), was isolated. Treatment of compound **3a** with BBr_3, followed by MeI, afforded the desired product **2a**. The structural novelty of intermediate **3a** intrigued us to explore the process with more care. It was later found that boronic acid **SM-1** could be converted to **3a** even in the absence of AgOTf. We hypothesized that the benzo[*b*]furan boronic acid, due to its poor stability, could be converted to compound **1a** under the basic conditions, followed by reaction to **3a**. The hypothesis was further proven that **1a** could be directly converted to **3a** by Selectfluor.

Scheme 1 Different methods according to the references



Scheme 2 Method explored according to Ritter's paper

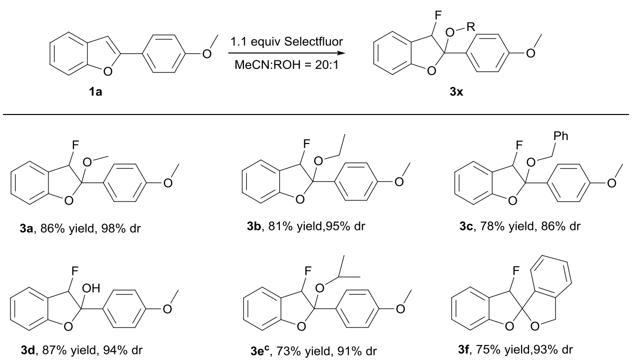


The transformation from benzo[*b*]furan **1a** to **3a** was well adapted to a variety of oxygen nucleophiles, including different alcohols and even water (**3d**), as shown in Table 1. Interestingly, a spiroacetal structure (**3f**) was obtained through intramolecular nucleophilic addition if a tethered oxygen nucleophile was present. Other nucleophiles, such as PhCOOH, $BnNH_2$ and CH_3NH_2, have also been investigated; however, the desired products were not observed.

Fluorinations of indoles have been reported in recent years.[20]

With Selectfluor, indoles can be either monofluorinated[21] or difluorinated.[22] Unlike the indoles, benzo[*b*]furans cannot be difluorinated, even with two or more equivalents of Selectfluor. In addition, benzofuran cannot be monofluorinated in the absence of water or other nucleophiles.

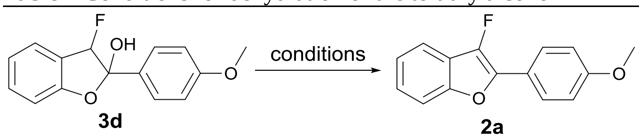
Table 1 Fluorination of **1a** using alcohols and water as nucleophiles [a, b]



[a] The reaction was run on a 0.5 mmol scale under air. For details, see the ESI. [b] Isolated yield. [c] 1.0 eq $NaHCO_3$ was added

To obtain the desired fluorinated benzo[*b*]furans, we further investigated the conditions for dehydration of the tertiary alcohol (Table 2). BBr_3 (entry 1) could successfully perform the dehydration in 72% yield, while other acids, such as TsOH H_2O, H_2SO_4, and HCl (entries 2 – 5) led to various by-products with the formation of **2** in poor yields. Therefore, we explored basic conditions to remove the tertiary alcohol, such as MsCl/Et_3N, MsCl/Py, $(CF_3SO_2)_2O$/Py, and $SOCl_2$/Py. To our delight, the dehydration of the tertiary alcohol under $SOCl_2$/Py conditions was very clean with a satisfactory yield of fluorinated benzo[*b*]furan **2**.

Table 2 Conditions for dehydration of the tertiary alcohol [a, b]

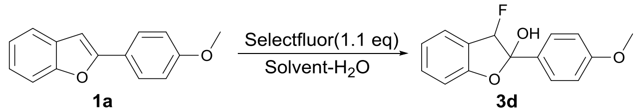


Entry	Reagent	Solvent	Temperature /time	Yield (%)	By-product (%)[c]
1	BBr_3	DCM	0 °C/30 min	72	15
2	TsOH H_2O	DCM	rt/3 h	-	-
3	TsOH H_2O	toluene	100 °C/1 h	71	21
4	H_2SO_4	dioxane	100 °C/2 h	messy	-
5	HCl	dioxane	100 °C/2 h	messy	-
6	MsCl/Et_3N	DCM	rt/18 h	Very little	-
7	MsCl/Py	DCM	rt/18 h	Very little	-
8	$(CF_3SO_2)_2O$	DCM	rt/18 h	Very little	-
9	$SOCl_2$/Py	DCM	rt/18 h	85[b]	<2

[a] The reaction was run on a 0.3 mmol scale, **3d** was about 90% purity. [b] Isolated yield. [c] NMR yield. [d] This experiment has been carried out for three trials.

Subsequently, the reaction was further investigated by screening various parameters (Table 3). The results indicated that the choice of solvent, the amount of H_2O and the temperature were important for the yield of **2a.** The best solvent for this reaction was MeCN, while other solvents, such as DMF, acetone, DMSO and DCM, gave unsatisfactory yields. The optimal ratio of MeCN/H_2O is 20:1. In our experience, more water led to poor solubility of **1a**, while a lesser amount of water made the reaction slow down. To avoid the considerable side reactions, the best temperature for the reaction was 25 ˚C.

Table 3 Optimization of the reaction of 2-(4-methoxyphenyl)benzofuran (**1a**) with Selectfluor [a, b]

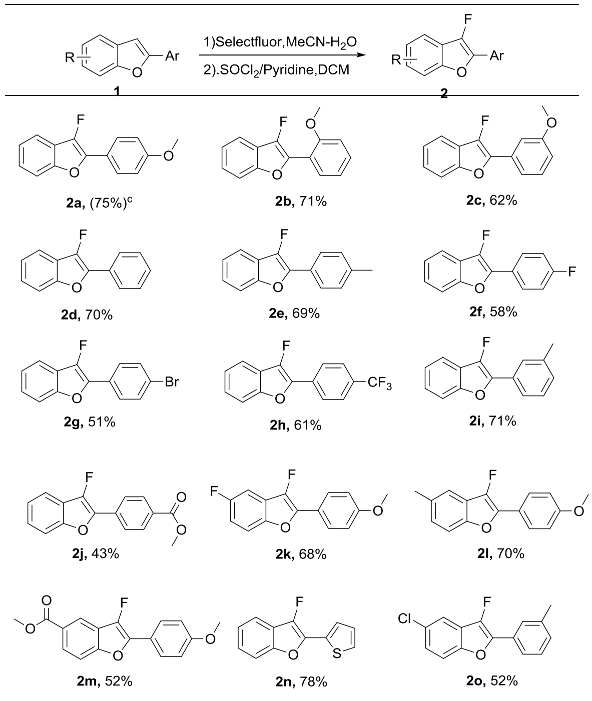


Entry	H2O	Solvent	Temperature/time	Yield (%)[b]
1	-	MeCN	25 °C/2 h	<10
2	1 equiv	MeCN	25 °C/2 h	52
3	3 equiv	MeCN	25 °C/2 h	62
4	5 equiv	MeCN	25 °C/2 h	65
5	1/20 solvent	MeCN	0 °C/1 h	56
6	1/20 solvent	MeCN	25 °C/1 h	87
7	1/4 solvent	MeCN	25 °C/1 h	75
8	1/20 solvent	DCM	25 °C/5 h	25
9	1/20 solvent	DMF	25 °C/5 h	42
10	1/20 solvent	acetone	25 °C/5 h	48

[a] Reaction conditions: **1a** (0.2 mmol), Selectfluor (1.1 equiv), solvent (2 mL), **3d** was about 90% purity. [b] Isolated yield. [c] NMR yield. [d] This experiment has been carried out for three trials.

We next examined the reaction scope. As shown in Table 4, various 2-arylbenzo[*b*]furans substituted with both electron-donating and electron-withdrawing functional groups (e.g., ether, halogen, ester, CF_3) were applied to the reaction. Most of the reaction intermediates could not be purified by silica gel chromatography, most likely due to the instability of the tertiary alcohol under the acidic silica gel conditions. Therefore, the tertiary alcohol generated from the first step was directly removed under the basic conditions to afford the corresponding 3-fluorinated benzo[*b*]furans. The total yields ranged from 43% to 78%, as shown in Table 4.

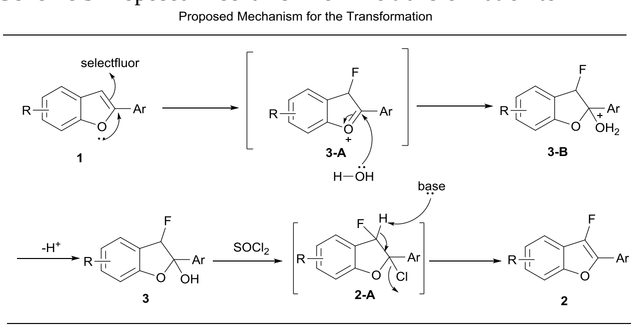
Table 4 Scope of the 3-fluorination of 2-substituted benzo[*b*]furans [a, b]



[a] The reaction was run on a 0.5 mmol scale under air. For details, see the ESI. [b] Isolated yield. [c] Scale up reaction was run on 10 mmole scale

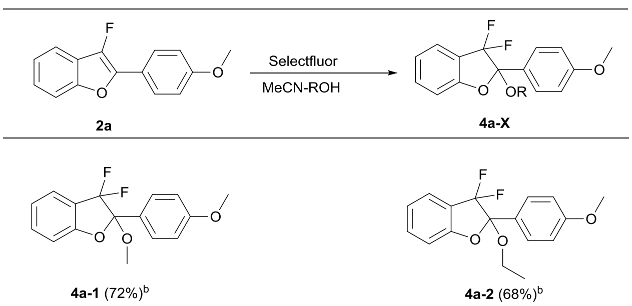
Based on the results above, the mechanism of this transformation is proposed (Scheme 3). Initially, reaction of **1** with Selectfluor yields the unstable cation **3-A**, which is then attacked by water to form **3-B**. After deprotonation, **3** is subject to chlorination and elimination to give benzo[*b*]furan **2**.

Scheme 3 Proposed Mechanism for The transformation to **2**



Finally, 3,3-difluorobenzofurans were investigated using the same protocol, and the desired 3,3-difluorobenzo[*b*]furans were also produced in satisfactory yields (Table 5).

Table 5 Difluorination of **2a** using alcohols as nucleophiles [a, b]



[a] Reaction conditions: **2a** (0.5 mmol), Selectfluor (0.55 mmol, 1.1 eq), MeCN-ROH=(8 mL-0.4 mL), 2h. [b] Isolated yields

Conclusions

In summary, we have developed an efficient method for the synthesis of 3-F-substituted 2-arylbenzo[*b*]furans. In this method, the benzo[*b*]furan ring was fluorinated with high regioselectivity at the C3 carbon with Selectfluor. Additionally, the mild conditions and practical convenience would make it a valuable synthetic tool to enrich structural diversity in organic chemistry. The biological evaluation of these novel compounds is underway in our laboratory and will be reported in due course.

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Notes and references

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/b000000x/

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