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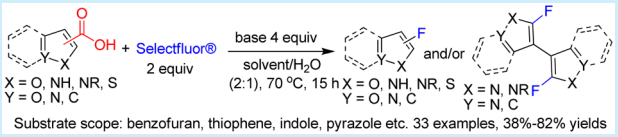
Decarboxylative Fluorination of Electron-Rich Heteroaromatic Carboxylic Acids with Selectfluor

Xi Yuan, Jian-Fei Yao, and Zhen-Yu Tang*

Department of Pharmaceutical Engineering, College of Chemistry and Chemical Engineering, Central South University, Changsha 410083, China

Supporting Information

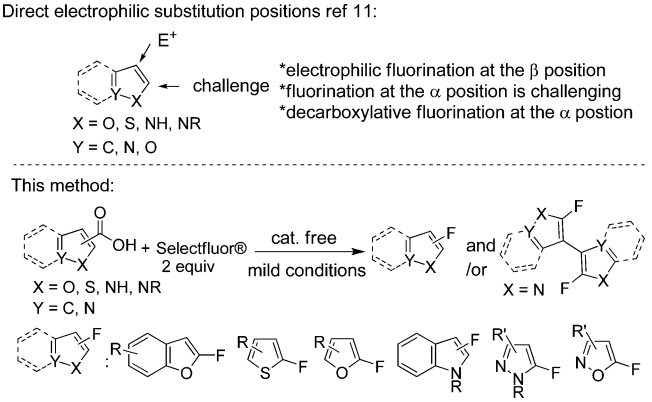
ABSTRACT: A transition-metal-free decarboxylative fluorination of electron-rich five-membered heteroaromatics, including furan-, pyrazole-, isoxazole-, thiophene-, indole-, benzofuran- and indazolecarboxylic acids, with Selectfluor is reported. Fluorinated dimer products were observed for nitrogen-containing heteroaromatic carboxylic acids, such as indole and pyrazole. An effective method has been developed to synthesize the monomer of 2- and 3-fluoroindoles with Li_2CO_3 as base at low temperature.



Incorporation of fluorine into a target molecule has a considerable impact on the molecule's reactivity, selectivity, biological activity, and physical properties.[1] This is especially true in medicinal chemistry, where fluorine is often employed as a bioisostere of hydrogen and where many important drug compounds also feature heteroaromatic rings.[2] Fluorine-containing, electron-rich, five-membered heteroarenes have been widely investigated in agrochemical, pharmaceutical, and material sciences.[3] For example, penflufen is 5-fluoropyrazole with antifungal/antimicrobial properties in plant protection.[4] Early development of decarboxylative fluorination of alkyl carboxylic acids employed toxic F_2 or XeF_2.[5] Recently, various elegant examples of decarboxylative fluorination of C_{sp3} carboxylic acids have been developed as effective methods to construct C−F bonds. For example, the groups of Sammis, Li, Gouverneur, Groves, MacMillan, and Ye have developed decarboxylative fluorination of alkyl or aryloxy carboxylic acids by Hunsdiecker-type fluorination and photofluorination.[6−8] The Hu and Hartwig groups greatly extended scope of this reaction to generate trifluoromethyl aryl ethers.[9] Our group has developed a transition-metal-free decarboxylative fluorination of cinnamic acids.[10] Despite these remarkable advances in decarboxylative fluorination of C_{sp3} carboxylic acids, general methods for C_{sp2}, such as aryl and heteroaromatic, carboxylic acids, remains less developed.

Selective introduction of fluorine to the different sites of heteroarenes represents another challenge in synthesis. For example, direct electrophilic fluorination of electron-rich heteroarenes normally occurs at the β-position (Scheme 1).[11] It is of great interest to develop a new strategy to install fluorine at the α-position of five-membered heteroarenes, which cannot be accessed by electrophilic substitution. Herein, we disclose a general decarboxylative fluorination of a broad range of furan-, pyrazole-, isoxazole-, thiophene-, indole-, benzofuran-, and indazole-2- and 3-carboxylic acids with inexpensive, bench stable, and commercially available Selectfluor under mild conditions. This method, to the best of our knowledge, represents the first general method for decarboxylative fluorination of aryl carboxylic acids.

Scheme 1. Decarboxylative Fluorination Strategy of Electron-Rich Heteroarenes



Our study commenced with the model reaction between benzofuran-2-carboxylic acid **1a** and Selectfluor (Table 1).[12,13] Transition-metal-catalyzed methods (entry 1), including those of Li et al.,[7a] hardly resulted in formation of the desired product **2a**, presumably because of Ag(I) or Cu(I) metal coordination to the heteroatom and the neighboring carboxylic group to form insoluble silver or copper carboxylate.[8a] We found that simply mixing **1a** with Selectfluor at 70 °C in acetonitrile (MeCN) and water (2:1) afforded a 35% yield (entry 2). Screening of solvents showed that hydrophobic solvents such as ethyl acetate and cyclohexane were better than hydrophilic solvents, such as THF and dioxane (entries 5−10 vs 2−4). Neither pure organic solvent nor pure water as solvent provided any desired product. Weak bases were better than

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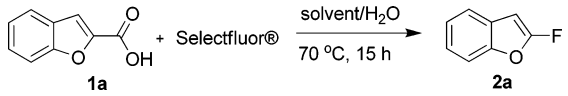
Org. Lett. XXXX, XXX, XXX−XXX

Table 1. Optimization of Decarboxylative Fluorination of Benzofuran-2-carboxylic Acid[a,b]



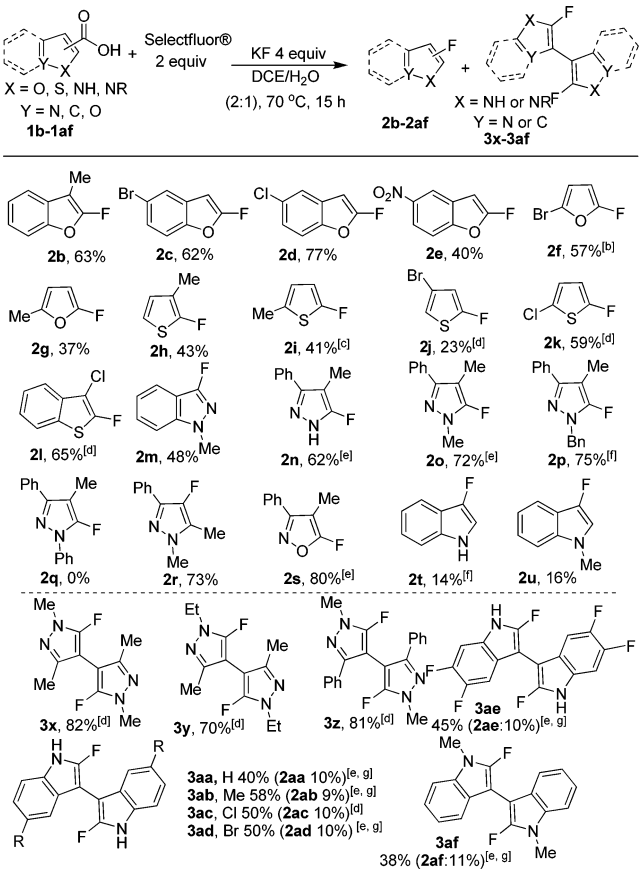
entry	solvent	base	yield (%)
1[c]	MeCN	none	0
2	MeCN	KF	34
3	THF	KF	57
4	dioxane	KF	39
5	toluene	KF	46
6	hexane	KF	48
7	cyclohexane	KF	63
8	ethyl acetate	KF	67
9	CH_2Cl_2	KF	75
10	**DCE**	**KF**	**79**
11	DCE	NaF	52
12	DCE	CsF	37
13	DCE	NaOH	4
14	DCE	LiOAc	71
15	DCE	Li_2CO_3	19
16	DCE	Li_3PO_4	61
17	DCE	$NaHCO_3$	22
18	DCE	HCOONa	71
19	DCE	NaCl	39
20	DCE	none	35
21[d]	DCE	KF	0
22[e]	DCE	KF	72
23[f]	DCE	KF	77

[a]Conditions: **1a** (0.2 mmol), Selectfluor (0.4 mmol), base (0.8 mmol), solvent/H_2O (0.6 mL:1.2 mL), 70 °C, 15 h. [b]^{19}F NMR yield based on 4-fluorotoluene as internal standard. [c]10% $AgNO_3$ as catalyst. [d]NSFI or NFPY as fluorinating reagent. [e]50 °C. [f]90 °C.

strong bases such as sodium hydroxide, which led to Selectfluor decomposition. Further optimization with different lithium, sodium, and potassium bases revealed potassium fluoride (entries 10−19) as the best base with 79% yield. Alternative electrophilic fluorination reagents, such as *N*-fluorobenzenesulfonimide (NSFI) and 1-fluoropyridium tetrafluoroborate (NFPY), produced no product for this transformation (entry 21). At last, reactions at different temperatures were tested, and 70 °C was proved to be the best temperature (entries 23 and 24) for substrate **1a**. Overall, the optimal combination of base and solvent was the key for this reaction.

With the optimized conditions in hand, we explored the substrate scope with different combinations of base, solvent, and temperature. As summarized in Scheme 2, a range of electron-rich heteroarenes, such as furan-, pyrazole-, isoxazole-, thiophene-, indole-, benzofuran-, and indazolecarboxylic acids, successfully underwent decarboxylative fluorination with Selectfluor. Benzofuran-2-carboxylic acids with both electron-rich (**1b**) and electron-deficient (**1c−e**) substitutions were readily fluorinated with satisfactory yields (40%−77%). 2-Furancarboxylic acids (**1f** and **1g**) were fluorinated smoothly as seen, but the reaction of **1f** reacted much faster than **1g**, and the reaction had to be limited to 7 h in cyclohexane at room temperature. Either elongation of reaction time or increased temperature reduced the yield. Both electron-donating (**1h** and **1i**) and electron-withdrawing substrates (**1j** and **1k**) of thiophene-2-carboxylic acids underwent the fluorination with modest yields in cyclohexane. Only one example of

Scheme 2. Decarboxylative Fluorinations of Furan-, Thiophene-, Benzofuran-, Isoxazole-, Pyrazole-, and Indolecarboxylic Acids[a]



[a]Conditions: **1** (1 mmol), Selectfluor (2 equiv), KF (4 equiv), DCE 3.3 mL, H_2O 1.7 mL, 70 °C, 15 h, isolated yields. [b]Cyclohexane as solvent, rt, 7 h. [c]Yields determined by ^{19}F NMR with 4-fluorotoluene as internal standard. [d]Cyclohexane as solvent. [e]LiOAc as base. [f]LiOAc as base, EtOAc as solvent. [g]Minor product yields lower than 10% determined by ^{19}F NMR.

benzothiophene-2-carboxylic acid (**1l**) resulted in the formation of desired product (**2l**, 65%). Methyl-protected indazole-3-carboxylic acid **1m** served as the sole example of pyrazole-3-carboxylic acids to accomplish this transformation successfully. Fully substituted pyrazole-5-carboxllic acids with different protecting groups (**1n−q**) were tested. Substrates with electron-rich protecting groups such as methyl and benzyl groups provided slightly higher yields than unprotected ones. However, the phenyl-protected substrate (**1q**) did not afford any product. Fully substituted pyrazole-4-carboxylic acid (**1r**) was fluorinated with satisfactory yield, although pyrazole-3-carboxylic acids with similar structures did not work for this strategy. In the meantime, the decarboxylative fluorination of isoxazolecarboxylic acids only occurred on the 5-position (**1s**). Decarboxylative fluorination of indole-3-carboxylic acids (**1t** and **1u**) resulted in multiple products with low yields due to the thermal instability of 3-fluoroindole at 70 °C in the basic solution.[14] Various 3-substituted pyrazole-5-carboxylic acids, including methyl-/ethyl-protected and phenyl-substituted, formed 5-fluorinated dimer products (**3x−z**) as the only products with a 4,4′-linkage in remarkable yields (70%−82%) in cyclohexane. Decarboxylative fluorination of both unprotected and methyl-protected indole-2-carboxylic acids (**1aa−af**)

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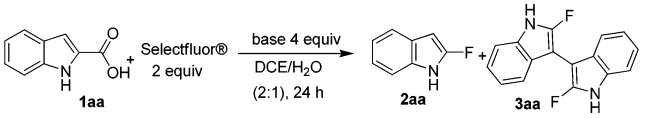
Org. Lett. XXXX, XXX, XXX−XXX

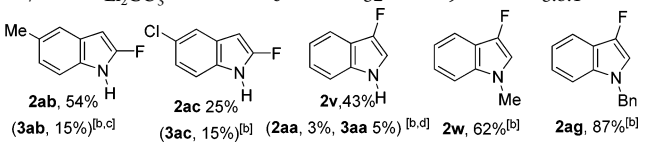
resulted in primarily 3,3′-linked dimers (**3aa**−**af**, 40%−58%) and less than 10% monomeric product (**2aa**−**af**) with LiOAc as base. Substrates with an electron-donating group produced slightly higher yields than the substrates with electron-deficient groups.

Although the decarboxylative fluorinations of indolecarboxylic acids were successful, the major products, 3,3′-linked fluoroindoles, have limited applications in the synthetic field. In addition, the yields of sensitive 3-fluoroindoles are relatively low under current conditions. We began efforts toward the syntheses of monomeric 2-fluoroindole with indole-2-carboxylic acid **1aa** as the model compound (entry 1, Table 2). Different

Table 2. Syntheses of 2-Fluoroindole Monomers



entry	base	temp (°C)	yield (%) 2aa	3aa	ratio (2aa/3aa)
1[a]	LiOAc	70	10	40	1:4.0
2[a]	Li_3PO_4	70	18	31	1:1.7
3[a]	NaF	70	16	30	1:1.9
4[a]	$NaHCO_3$	70	29	18	1.6:1
5[b]	$NaHCO_3$	0	45	13	3.5:1
6[b]	Na_2CO_3	0	49	10	4.9:1
7[b]	Li_2CO_3	0	52	9	5.8:1



[a]Standard conditions: 0.2 mmol scale, solvent/H_2O (1.2 mL/0.6 mL), Selectfluor (0.4 mmol), base (0.8 mmol), 70 °C, 24 h. [b]Li_2CO_3 as base, 0 °C. [c]MeCN as solvent. [d]EtOAc as solvent.

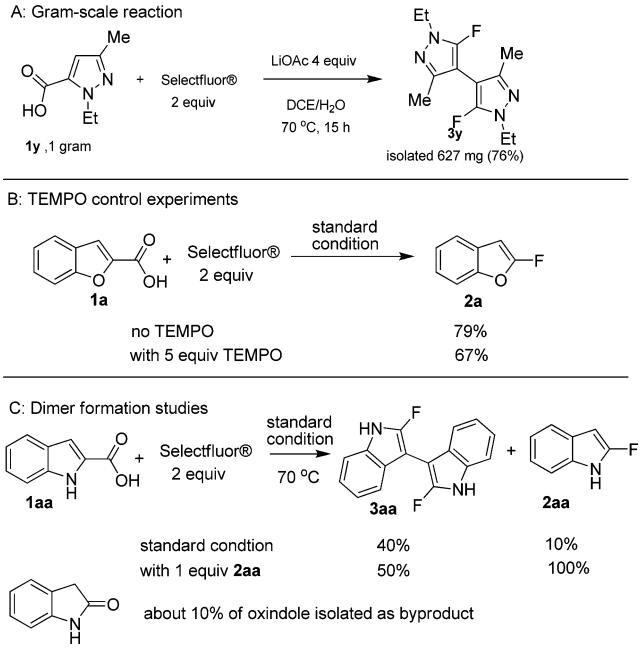
bases were extensively screened (see Table S3). Lithium and sodium bases were identified as base choices to increase the selectivity (entries 2−4). Lowering the temperature to 0 °C with lithium carbonate afforded the best selectivity of 5.8:1 (entry 7) and higher combined yields (62% vs 50%, entry 7 vs 1). Various indole-2- or -3-carboxylic acids were tested with Li_2CO_3 as base at 0 °C.

Electron-rich indole-2-carboxylic acids **1ab** resulted in better selectivity and combined yields than electron-deficient substrate **1ac**. For the unstable 3-fluoroindole syntheses, the low-temperature method greatly improved both the selectivities and yields (**2v**, **2w**, and **2ag**). As an example, the decarboxylative fluorination of benzyl group protected indole-3-carboxylic acid produced the desired **2ag** as the sole product with 87% yield.

The ability to conduct the decarboxylative fluorination on a gram scale was accessed. The fluorination of ethyl-protected pyrazole 5-carboxylic acid **1y** on a 1 g scale produced 627 mg of 4,4′-linked dimerized product **3y** (76% yield, Scheme 3A).

Silver-catalyzed Hunsdiecker-type and photocatalyzed decarboxylative fluorinations of alkyl or aryloxy carboxylic acids involve organic radical intermediates and electrophilic fluorinating reagents. However, it is not easy for aryl carboxylic acids to generate aryl radicals through a decarboxylative strategy. To investigate the mechanism, a series of control experiments were

Scheme 3. Mechanistic Insights



conducted. Radical scavenger TEMPO did not significantly affect the yield under standard conditions (Scheme 3B). This result is contrary to our previously reported decarboxylative fluorinations of cinnamic acids.[10] Due to the biphasic nature of our methods, TEMPO might stay in the organic phase, which is a hydrophobic solvent. Selectfluor is liberated from the effect of TEMPO with the deprotonated heteroaromatic acids in the aqueous phase, where both decarboxylation and fluorination occur. After the reaction, the fluorinated products were extracted into the organic phase. ^{19}F NMR studies revealed no fluorinated intermediates except Selectfluor in the aqueous phase and the desired products in the organic phase (see Supporting Information). In the dimer formation control experiment, the presence of 2-fluoroindole (**2aa**) did not improve the dimer yield and was not consumed under standard conditions (Scheme 3C), which implied that 2-fluoroindole was unlikely the starting material for formation of dimer **3aa** through Friedel−Crafts-type dimerization. In addition, we isolated about 10% of oxindole as the byproduct. ^1H NMR studies demonstrated that the formation of oxindole was in proportional to the formation of fluorinated dimer product, which implied they might go through a similar reaction pathway. From kinetic studies, oxindole was not consumed in the reaction and cannot be intermediate. The literature demonstrated that treatment of indole-2-carboxylic acid with electrophilic chlorinating reagents afforded 3,3-dichloro-oxindole after decarboxylation.[15] Selectfluor acts not only as an initiator of electrophilic decarboxylation but also as a fluorinating agent for the decarboxylative fluorination. However, the mechanism of this transformation remains unknown and requires further investigation.

In conclusion, we have developed the first general method for decarboxylative fluorination of aryl carboxylic acids. Selectfluor and the combination of base, solvent, and temperature were the keys for the decarboxylative fluorination of electron-rich heteroaromatic carboxylic acids such as furan-, pyrazole-, isoxazole-, thiophene-, indole-, benzofuran-, and indazolecarboxylic acids under mild conditions. Efforts to

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Org. Lett. XXXX, XXX, XXX−XXX

achieve other decarboxylative functionalizations of heteroaromatic carboxylic acids are ongoing.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.7b00335.

Experimental procedures, mechanistic studies, compound characterization,and spectroscopic data (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: zytang@csu.edu.cn.

ORCID

Zhen-Yu Tang: 0000-0002-3972-5047

Notes

The authors declare no competing financial interest.

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