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Selective C4–F bond cleavage of pentafluorobenzene: synthesis of N-tetrafluoroarylated heterocyclic compounds

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ABSTRACT

A simple aromatic nucleophilic monosubstitution reaction for the synthesis of N-tetrafluoroarylated heterocyclic compounds via selective C4–F bond cleavage of pentafluorobenzene with N–H containing heterocycles is demonstrated. This method is highly tolerant of a wide range of substrates to give the corresponding products in moderate to good yields. Additionally, this strategy is applied to synthesize other mono-, di-, and tri-fluoroarylated indole derivatives.

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The incorporation of fluorine or fluorine-containing groups into organic molecule has received intensive attention due to the unique effect of F-substituents in material science and the pharmaceutical industry.[1] While pentafluorobenzene is considered to be a representative class of such fluorinated compounds which could be transformed to other fluorine-containing compounds through a series of reactions.[2] To date, elegant achievements of the functionalization of pentafluorobenzene have been made on the direct arylation, alkenylation, and alkylation.[3] Yet, these pioneering and intriguing works are mainly focused on the C–H activation of pentafluorobenzene. The carbon–fluorine bond is known as the strongest single bond, and its activation/cleavage has attracted an increasing interest because such a process offers great potential in the preparation of bioactive compounds. Despite the C–F cleavage reactions (intermolecular or intramolecular C–F cleavage) of pentafluoroarenes and other fluoroarenes have emerged, most of them were carried out in the presence of the transition-metal catalysts.[4] For instance, the Johnson group has successfully developed an efficient method for selective C–F bond activation of tetrafluorobenzenes by Nickel with an analogous nitrogen donor.[3f] Well-designed nickel-based catalytic strategy reported by the Radius group enables us to produce new C–C bonds via selective C–F activation of polyfluoarenes.[5] And recently, the Nakamura group has made an outstanding advance on finding a diphosphine-assisted transition metal catalyst, which allows us to create partially fluorinated arenes.[4j] Although these significant advances have been achieved, the development of metal-free methods for the direct cleavage of C–F bond of pentafluoroarenes is highly desirable.

N-arylated heterocycles are key intermediates in the synthesis of many biologically-active compounds[6] and great efforts have been made for their constructions. The transition-metal catalyzed Ullmann-type reaction is one of the traditional methods for the preparation of N-arylated heterocyclic compounds,[7] but usually these protocols suffer from some drawbacks, such as higher reaction temperature, long reaction time, tedious procedures for the preparation of ligands,[8] toxicity of some catalysts,[9] and waste disposal issues arising from the use of excess catalysts,[10] which inhibit their wide applications in the construction of complex molecules. Apart from the transition-metal-catalyzed strategy, nucleophilic aromatic substitution reactions,[4h,11] or coupling with organometallic reagents[12] are two alternatives for the N-arylation reactions. Yet, these efficient methods are suitable for substrates of aryl chlorides, aryl bromides, or aryl iodides. At present, although there are reports on the C–N bond formation via C–F bond cleavage of aryl fluorides with N–H containing compounds,[13] the C–N formation of indoles with pentafluorobenzene via C4–F bond cleavage based on the S_NAr reaction still remains untouched. Moreover, among N-arylated heterocycles, the *N*-fluoroaryl substituted structure-units, especially the indole derivatives, are considered to be important building blocks in some pharmaceutical molecules.[14] Thus, the search for simple and effective approaches to synthesize *N*-fluoroaryl substituted indole derivatives is of special interest. Herein, we report a milder (70 °C), rapid (mostly within two hours), operational, and efficient protocol for the synthesis of N-tetrafluoroarylated heterocyclic compounds via selective C4–F

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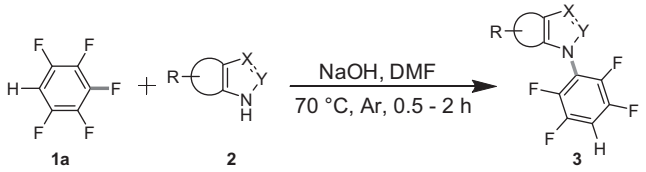
bond cleavage of pentafluorobenzene with diverse N–H heterocycles. With this method, a series of products were furnished in high yields (up to 88%), which might contribute to the synthesis of some pharmaceuticals.

Pentafluoroarenes are known to be electron-deficient compounds.[3] We speculated that electron-rich groups like organic anions may attack pentafluoroarenes through the S_NAr reaction to produce new compounds. It has been reported that the N–H of indole was able to form N^- anion in basic medium.[15] Initially, we examined the reaction of pentafluorobenzene **1a** with indole **2a** in DMSO at 90 °C under Ar atmosphere. Surprisingly, we found that the presence of NaOH (2 equiv) resulted in the formation of product **3a** in 81% yield, which suggested that the cleavage of C4–F bond occurred. No detectable amount of **3a** was observed in the absence of NaOH, thus indicating the reaction is an alkali-driven process. Encouraged by this preliminary result, a survey of reaction parameters including bases and solvents was conducted (Table S1 in the Supporting information). NaOH and DMF were found to be the optimal. Other bases and solvents were less or not active. Under the selected conditions of base and solvent, a brief optimization for the reaction temperature, time, and the loading of base was carried out. Gratifyingly, when the reaction of **1a** and **2a** was performed in the presence of 1.0 equiv of NaOH as base, 2.0 mL of DMF as solvent at 70 °C for 1 h under Ar, product **3a** was obtained in 86% yield.

With the optimal conditions, we investigated the substrate scope of N–H-containing heterocyclic compounds. Both electron-donating groups such as methyl, ethyl, and methoxy (Table 1, **3b**–**f**) and electron-withdrawing groups such as chloro, bromo, and acetyl (Table 1, **3g**–**j**) on the aryl ring of indoles were all tolerated under the selected conditions, and moderate to good yields of the corresponding S_NAr products were obtained. In addition, for methyl-substituted substrates, good results could be obtained no matter where the methyl group lay (Table 1, **3b**, **3c**, and **3e**). During this reaction, chloro and bromo groups are inactive (Table 1, **3h**–**j**), obviously different from the reported transition-metal catalyzed coupling reaction.[6–9] The presence of chloro or bromo groups in the products provided a good opportunity for later creation of

Table 1
N-polyfluoroarylated heterocyclic compounds derived from N–H-containing heterocycles with pentafluorobenzene[a]



1a 2 3

3a, 86% 3b, 88% 3c, 81% 3d, 80%

3e, 69% 3f, 71% 3g, 66% 3h, 83%

3i, 83% 3j, 84% 3k, 78% 3l, 76%

3m, 73% 3n, 82% 3o, 83% 3p, 67%[b]

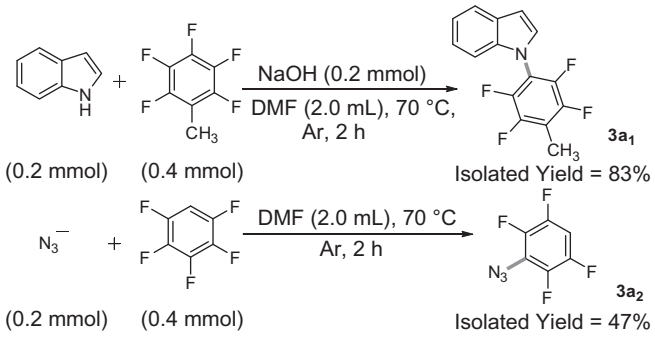
3q, 77%[b] 3r, 68%[b]

[a] Reaction conditions: **1a** (0.4 mmol), **2** (0.2 mmol), and NaOH (0.2 mmol) were added in DMF (2.0 mL) with stirring at 70 °C for 0.5–2 h. Yield: isolated yield.

[b] The reaction was conducted in 6 h.

new bonds. The other N–H heterocycles such as pyrrole, imidazole, piperazine, indazole, carbazole, and azaindole also served as suitable coupling partners in acceptable yields (Table 1, **3k**–**r**). Furthermore, to demonstrate the synthetic application of this methodology, a 0.5-g-scale synthesis of **3a** could also be performed in good yield (80%), indicating the good reliability of the process. Note that most of the products were isolated in the form of white solids. In some cases, in addition to the NMR, IR, and HRMS analyses, the structure of products **3g** was analyzed by the single-crystal X-ray technique (see the Supporting information).

To gain some insight into the reaction mechanism of **1a** with **2**, we carried out several control experiments (Scheme 1). To our delight, good result (83% yield of $\mathbf{3a_1}$) was accessed when **2a** reacted with 2,3,4,5,6-pentafluorotoluene under the standard conditions, thus suggesting that C–N forming reaction between **1a** and N–H heterocycles proceeded by direct C4–F cleavage of pentafluorobenzene. To determine whether the C4–F cleavage was caused by the base only, ^{19}F and ^{1}H NMR spectra were examined (details see the Supporting information, Figs. S1 and S2). The ^{19}F and ^{1}H NMR spectra in Figures S1 and S2 clearly imply that the C4–F cleavage of **1a** is not directly attributed to the presence of the base, that is, the nucleophilic attack of nitrogen is essential for this facile reaction.



Scheme 1. Control experiments.

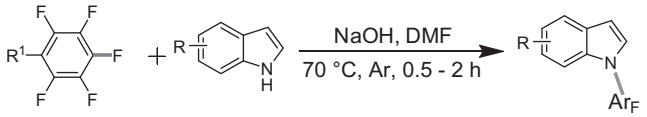
In addition, NaN_3 with electron-rich N_3^- was found to react with pentafluorobenzene to form $\mathbf{3a_2}$ in the absence of base (Scheme 1), further confirming that the nucleophilic attack of N^- anion can induce the cleavage of C4–F bond of **1a** and then produce the S_NAr products. To further study the mechanism of **1a** and **2**, the reaction system was examined by NMR spectroscopy, but unfortunately, all the resonances in the NMR spectra originate from the reactants and product, that is, no information about the intermediates is detected in the time-dependent NMR spectra. This may be related to the quick formation and transformation of the intermediates. Based on our preliminary results, the reaction mechanism related to the nucleophilic substitution process is proposed (see the Supporting information, Scheme S1).

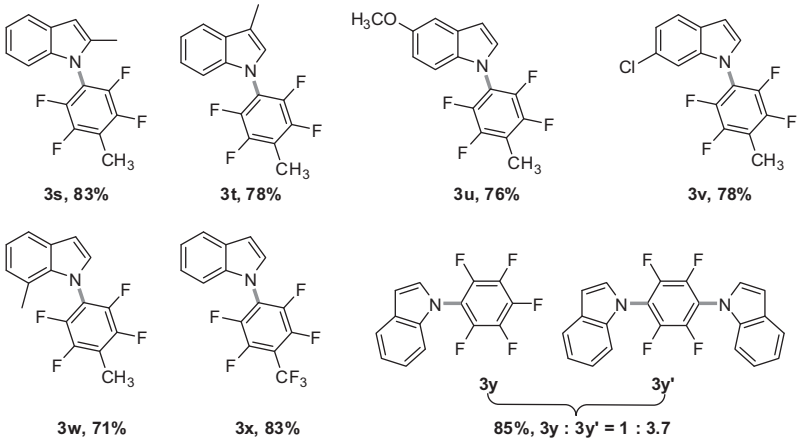
This metal-free method could afford the coupling products with other pentafluoroarenes (Table 2). For example, 2,3,4,5,6-pentafluorotoluene reacted with indoles to give the desired products in good yields regardless of the substituents on the indoles (**3a1**, **3s**–**w**). Octafluorotoluene and hexafluorobenzene also react with **2a** and produced the corresponding products in good yields, despite the later generation of a mixture of multiple coupling products (**3x**, **3y,** and **3y′**).

It was found that polyfluoroarene substrates could bear different numbers of fluorine atoms. For example, 2,3,5,6-tetrachloropyridine and 1,2,4-trifluorobenzene could smoothly undergo direct tri- and difluoroarylation of **2a** in good yields (Table 3, **4a**, **4b**). In addition, 1,4-difluorobenzene could also give the desired product (Table 3, **4c**), albeit in a slightly lower yield (36%). In all cases, the removal of F atoms in polyfluoroarenes is observed (Tables 1–3), confirming that the C–F cleavage occurs in this interesting reaction. However, fluorobenzene was unreactive under the standard condition adopted in this communication, which may be attributed to the electron-rich character of fluorobenzene. This fact further shows that the electron-deficiency of the aryl ring is important for this nucleophilic substitution reaction.

N-Tetrafluoroarylated heterocyclic compound is also versatile synthetic intermediate and could be readily transformed into other tetrafluoroarylated compounds (Scheme 2). In fact, **5** could not be obtained in high yield through the direct reaction of 1-(1*H*-indol-3-

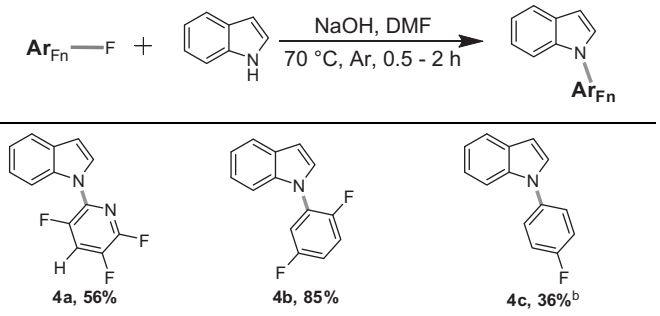
Table 2
N-Tetrafluoroarylation of indoles[a]





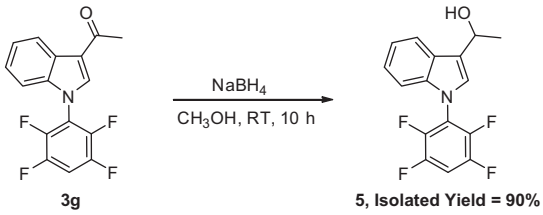
[a] Reaction conditions: indoles (0.2 mmol), NaOH (0.2 mmol), and pentafluoroarenes (0.4 mmol) were added in DMF (2.0 mL) with stirring at 70 °C for 0.5–2 h. Yield: isolated yield.

Table 3
Synthesis of other N-polyfluoroarylated products of indole[a]



[a] Reaction conditions: **2a** (0.2 mmol), NaOH (0.2 mmol), and polyfluoroarenes (0.4 mmol) were added in DMF (2.0 mL) with stirring at 70 °C for 0.5–2 h. Yield: isolated yield.

[b] The reaction was conducted with KOH (0.2 mmol) as base stirring at 90 °C, 24 h.



Scheme 2. Further synthetic transformation of the product.

yl)ethanol with **1a** using the standard condition that gave a mixture of the C–N and C–O formation products. But, the reduction of **3g** using a $NaBH_4$ at room temperature generated the corresponding reduced product **5** in high yield. The promising transformation indicated that our protocol provides a reliable approach for the synthesis of diverse tetrafluoroarylated compounds.

In summary, we developed a simple and effective aromatic nucleophilic monosubstitution approach for the N-tetrafluoroarylation of N–H containing heterocycles with pentafluorobenzene via selective C4–F bond cleavage. Preliminary mechanistic analyses suggested that the nucleophilic attack of electron-rich N^- anion was significant for C4–F cleavage of pentafluorobenzene and C–N bond formation. The strategy is highly tolerant of substrates of both polyfluoroarenes and N–H heterocycles, and is able to give the corresponding products in moderate to good yields within 0.5–2 h. This effective protocol might be a promising alternative to the existing methods and be helpful to the synthesis of the *N*-fluoroaryl substituted pharmaceutical structural units. Meanwhile, the products could be further transformed into other organofluorine compounds, which are otherwise difficult to be accessed. Efforts to expand the substrate scope and to get deeper insight in the mechanism are underway.

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Supplementary data

Supplementary data (experimental details and NMR spectra) associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.tetlet.2013.06.055.

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