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CHEMISTRY AN ASIAN JOURNAL Communication

Aromatic Substitution

Synthesis of Pinpoint-Fluorinated Polycyclic Aromatic Hydrocarbons: Benzene Ring Extension Cycle Involving Microwave-Assisted S_NAr Reaction

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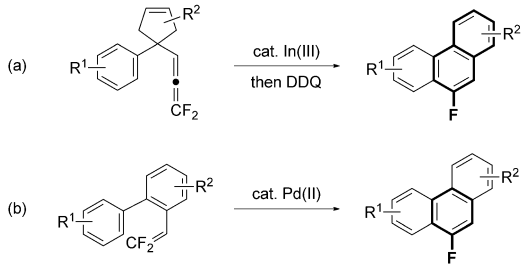
Abstract: Fluoroarenes bearing no electron-withdrawing groups (non-activated fluoroarenes) readily underwent nucleophilic aromatic substitution with α-cyanocarbanions under microwave irradiation. The sequence (i) formylalkylation involving the cyanoalkylation of fluoroarenes, (ii) difluorovinylidenation, and (iii) Friedel–Crafts-type cyclization, afforded extended fluoroarenes by one benzene ring per cycle. Furthermore, the performance of multiple cycles successfully provided higher-order pinpoint-fluorinated polycyclic aromatic hydrocarbons (F-PAHs).



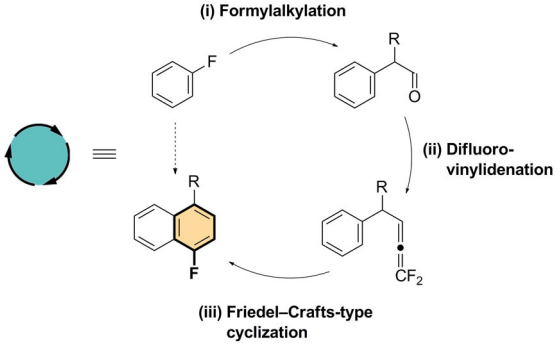
Scheme 1. F-PAH Syntheses.

Pinpoint-fluorinated PAHs (regioselectively fluorinated polycyclic aromatic hydrocarbons) are promising organic semiconducting materials[1] because of the unique properties of the fluorine substituent.[2] The high electronegativity of fluorine leads to an enhanced resistance of PAHs to aerial oxidation by lowering the energy level of their HOMO. In addition, the repulsive interaction between lone pairs in the fluorine 2p orbitals and the adjacent π electrons in the carbon 2p orbitals perturbs the electron density of the extended π systems,[3] which would render these compounds highly soluble in polar organic solvents, leading to printable organic electronics.[4] It is also worth mentioning the low steric impact of fluorine, whose introduction into PAH molecules should not change their molecular shape, would not significantly affect their π–π stacking in the solid structure.[5,6] Therefore, the effects of installing a single fluorine substituent in PAH skeletons would lead to advantageous semiconducting materials, such as THF-soluble fluorinated picenes, which exhibit p-type semiconducting behavior.[5,7]

To facilitate the efficient synthesis of pinpoint-fluorinated PAHs, we have recently developed metal-catalyzed cyclizations of fluoroalkenes on the basis of the following benzene ring construction strategy (Scheme 1): (a) 1,1-difluoroallenes, readily prepared via difluorovinylidenation of aldehydes,[8] undergo a Friedel–Crafts-type cyclization in the presence of a catalytic amount of indium(III) bromide.[9] Subsequent DDQ (2,3-dichloro-5,6-dicyano-*p*-benzoquinone) dehydrogenation affords pinpoint-fluorinated aromatic compounds (fluoroarenes). (b) These compounds were also accessible from 1,1-difluoroalkenes via a cationic palladium(II)-catalyzed cyclization (Scheme 1).[5,10,11]

As the preparation of the substrates for the indium(III)-catalyzed synthesis of pinpoint-fluorinated PAHs (i.e., difluoroallenes) involved fluoroarenes as starting materials, we envisioned a cyclic benzene ring extension strategy that would comprise the following steps (Scheme 2): (i) starting fluoroarenes would be subjected to formylalkylation via an S_NAr reaction to provide arylacetoaldehydes; (ii) the aldehydes would be then subjected to difluorovinylidenation;[8] finally, (iii) the Friedel–Crafts-type cyclization of the obtained 1,1-difluoroallenes[9] would furnish the benzene ring-extended fluoroarenes.

However, S_NAr reactions of fluoroarenes have been conducted on arenes activated by electron-withdrawing groups, including halogenes and trifluoromethyl groups,[12] and the S_NAr



Scheme 2. Benzene ring extension cycle.

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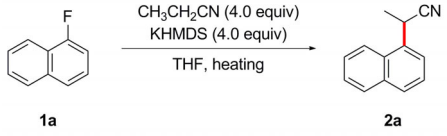
reactions of non-activated fluoroarenes have been limited to those on benzene π systems.[13] In the course of this study, we found that microwave irradiation[14] significantly facilitated the desired S_NAr reaction of non-activated fluoroarenes with naphthalene or higher-order PAH π systems (Table 1).[15] When fluoronaphthalene **1a** and propionitrile (4.0 equiv) were heated in

Table 1. Optimizations of S_NAr reaction.[a]



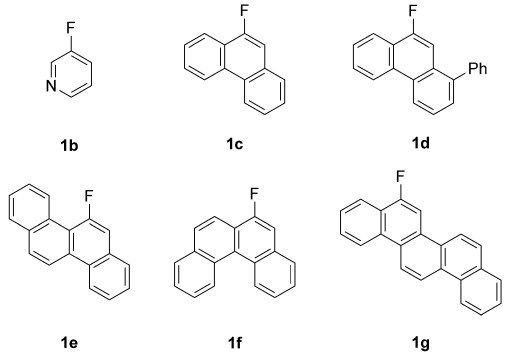
1a 2a

Entry	Heating	Concentration of **1a** [M]	Conditions	Yield of **2a** [%]
1	oil bath	0.25	65 °C, 24 h	6
2	oil bath	0.25	80 °C,[b] 16 h	17
3	microwave	0.25	80 °C,[b] 1 h	70
4	microwave	0.25	80 °C,[b] 1.5 h	77
5	microwave	0.50	80 °C,[b] 1.5 h	88 (82)

[a] ^{1}H NMR yield based on an internal standard (CH_2Br_2). Isolated yield in parentheses. [b] The reaction was conducted in a sealed vessel.

refluxing THF using a conventional oil bath in the presence of potassium bis(trimethylsilyl)amide (KHMDS, 4.0 equiv, entry 1), the desired alkylated naphthalene **2a** was obtained, albeit in low yields (6–17%, Table 1, entries 1 and 2). In contrast, microwave irradiation at 80 °C dramatically increased the yield of **2a** to 70% (entry 3). Further optimization afforded yields of up to 82% after isolation (entries 4 and 5).[16,17]

Acetonitrile (Table 2, entry 1) reacted with **1a** in a manner similar to that of propionitrile, affording the corresponding primary nitrile **2b** in 53% yield under microwave irradiation. In contrast, **2b** was not obtained when performing the S_NAr reaction of acetonitrile under oil bath heating (THF, reflux, 18 h). Decanonitrile, whose C8 alkyl chain is expected to enhance the solubility of PAHs, also afforded the corresponding naphthalene **2c** in 90% yield (entry 2). Thus, as well as secondary nitriles,[13a] acetonitrile and primary nitriles reacted with fluoronaphthalene under microwave irradiation. Isobutyronitrile, which is an effective substrate for nucleophilic aromatic substitution, gave **2d** in 92% yield (entry 3).

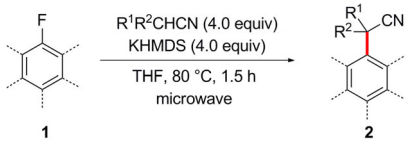


1b 1c 1d

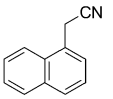
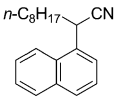
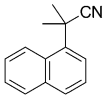
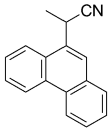
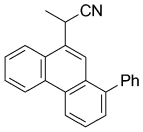
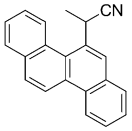
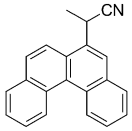
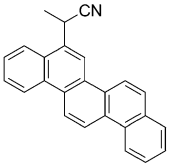
1e 1f 1g

Figure 1. List of fluoroarenes with extended π systems.

Table 2. Microwave-assisted S_NAr reaction.[a]



1 2

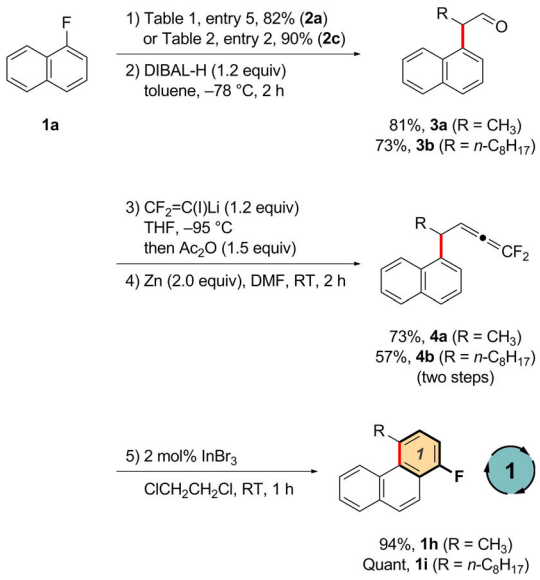
Entry	**1**[b]	R^1, R^2	Nitrile **2**		Yield [%][c]
1	**1a**	H, H		**2b**	53 (ND)
2	**1a**	n-C_8H_{17}, H		**2c**	90 (10)
3	**1a**	CH_3, CH_3		**2d**	92 (70)
4	**1b**[d]	CH_3, H		**2e**	54 (ND)
5	**1c**[d]	CH_3, H		**2f**	76
6	**1d**	CH_3, H		**2g**	93
7	**1e**[d]	CH_3, H		**2h**	70
8	**1f**[d]	CH_3, H		**2i**	89
9	**1g**[e]	CH_3, H		**2j**	92

[a] The reaction was conducted in a sealed vessel. [b] Unless otherwise noted, the concentration of **1** was 0.50 M. [c] Isolated yield. The yield obtained under oil bath heating (THF, 65 °C) is shown in parentheses. [d] **1** 0.25 M. [e] **1g** 0.008 M. ND = Not detected by ^{1}H NMR spectroscopy.

The microwave-assisted S_NAr reaction was applicable to a wide variety of fluoroarenes (Figure 1). Thus, 3-fluoropyridine (**1b**) afforded the corresponding product **2e** in 54% yield (Table 2, entry 4). Substitution of fluorophenanthrenes **1c** and **1d** also worked well to afford the corresponding **2f** and **2g** in 76 and 93% yields, respectively (entries 5 and 6). Fluorochrysene ([4]phenacene) **1e** and fluoro[4]helicene **1f** were successfully transformed into **2h** and **2i** in 70 and 89% yield, respec-

tively (entries 7 and 8), proving that substitution proceeded smoothly even at the bay region of the phenanthrene substructure of **1e**. Finally, fluoropicene ([5]phenacene) **1g** underwent substitution under identical conditions to give **2j** in 92% yield (entry 9). Thus, the scope of the microwave-assisted S_NAr reaction was expanded to include non-activated fluoroarenes with extended π systems.

With the microwave-assisted alkylation method in hand, we sought to explore its application to the planned benzene-ring extension (Scheme 3). Nitrile **2a**, obtained as detailed above



Scheme 3. Benzene ring extension of 1-fluoronaphthalene (1st cycle).

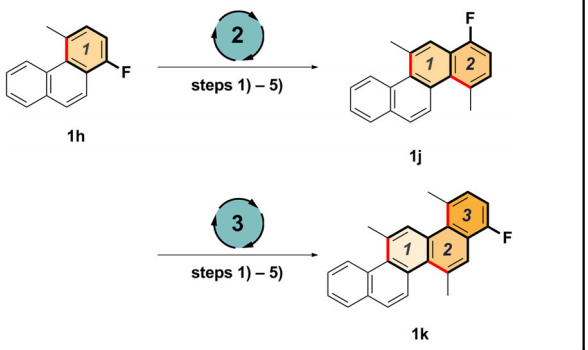
from **1a** (Table 1, entry 5: step 1, 82% yield), was subjected to half reduction with diisobutylaluminium hydride (DIBAL) to afford aldehyde **3a** in 81% yield (step 2). Difluorovinylidenation of **3a** afforded 1,1-difluoroallene **4a** in 73% yield over two steps (steps 3 and 4). Then, **4a** underwent Friedel–Crafts-type cyclization under indium(III) catalysis to provide fluorophenanthrene **1h** in 94% yield (step 5), thus completing the first cycle. In a similar manner, the benzene ring extension starting from **2c** afforded the corresponding **1i** in good yield.

By repeating the same protocol with fluoroarene **1h**, higher-order pinpoint-fluorinated PAHs were synthesized (Table 3). Thus, **1h** was subjected to the second ring extension to afford pinpoint-fluorinated chrysene **1j** (entry 1). The third ring extension of **1j** was performed to afford pinpoint-fluorinated picene **1k** (entry 2).

The benzene ring extension was successfully applied to not only terminal fluoroarenes but also internal ones (Scheme 4). Pinpoint-fluorinated triphenylene **1l** (top) was successfully synthesized from fluorophenanthrene **1c** via nitrile **2f**, whereas pinpoint-fluorinated triphenylene **1m** (bottom) was similarly obtained from fluorohelicene **1f** via **2i**.[18]

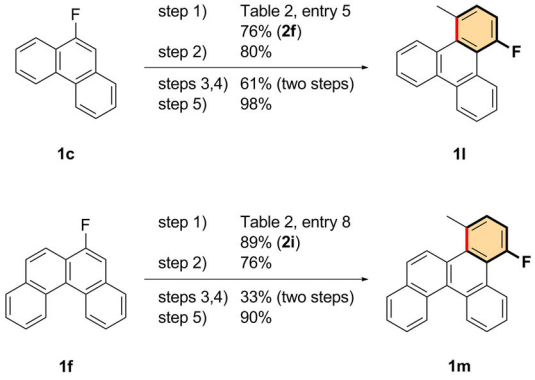
It is worth noting that the benzene ring extension using primary nitriles facilitated the synthesis of PAHs bearing a substituent in the bay region (Scheme 3, Scheme 4 and Table 3).

Table 3. Benzene ring extension of fluoroarenes (2nd and 3rd cycles) [a,b]



Entry	Cycle	Starting Compd	Yield [%] Step 1)	Step 2)	Steps 3,4)[c]	Step 5)
1	2nd	**1h**	71[d]	85	64	87, **1j**
2	3rd	**1j**	64[e]	79	36	79, **1k**

[a] Isolated yield. [b] For steps 1) to 5), see Scheme 3. [c] Two-step yield. [d] **1h** 0.5 M. [e] **1j** 0.25 M.



Scheme 4. Benzene ring extension of internal fluoroarenes.

Although effects of bay substitution are of importance not only from the viewpoint of organic devices but also from that of cancer research,[19] synthetic methods applicable to the molecules have been rare.[20] The benzene ring extension thus contributes to a wide range of research areas by providing the bay-substituted PAHs.

In summary, we have achieved a microwave-assisted S_NAr reaction of non-activated fluoroarenes with extended π systems. This S_NAr reaction along with difluorovinylidenation and cationic cyclization facilitated a benzene-ring-extension cycle, by which terminal and internal fluoroarenes were converted to the corresponding extended fluoroarenes in good yields. Thus, the cycle increases the variety of pinpoint-fluorinated PAHs.

Experimental Section

Microwave-assisted S_NAr reaction of non-activated fluoroarenes (step 1): The synthesis of nitrile **2a** is described as a typical procedure. To a THF solution (2.4 mL) of KHMDS (1.03 g, 4.80 mmol) was added 1-fluoronaphthalene (**1a**, 155 μL, 1.20 mmol) at room tem-

perature. After propionitrile (340 μL, 4.75 mmol) was added, the vessel was sealed and was irradiated using a microwave (65 W) at 80 °C for 90 min. The reaction mixture was poured into aqueous hydrochloric acid (2 M, 5 mL) at room temperature. Organic materials were extracted with EtOAc (3×4 mL). The combined extracts were washed with brine and dried over anhydrous sodium sulfate.

To the residue (396 mg) were added dibromomethane (109 mg) and α,α,α-trifluorotoluene (24 mg) as internal standards. Analysis by NMR spectroscopy indicated that nitrile **2a** was generated in 88% yield (by ^{1}H NMR based on CH_2Br_2) and fluoronaphthalene **1a** was consumed completely (by ^{19}F NMR based on CF_3Ph). The residue was purified by column chromatography on silica gel (*n*-hexane/EtOAc, 10:1) to give nitrile **2a** (178 mg, 82% yield) as a colorless liquid.

Half-reduction of nitriles (step 2): The preparation of aldehyde **3a** is described as a typical procedure. To a toluene solution (150 mL) of nitrile **2a** (28.2 g, 156 mmol) was added a toluene solution of diisobutylaluminium hydride (DIBAL-H, 1.00 M, 184 mL, 184 mmol) at −78 °C. After being stirred for 3 h at −78 °C, aqueous hydrochloric acid (6 M, 300 mL) was added and the mixture was allowed to warm to 0 °C. The mixture was filtered through a pad of celite using EtOAc as the eluent. The organic materials were extracted with EtOAc (3×50 mL). The combined extracts were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue was subjected to column chromatography on silica gel (*n*-hexane/ethyl acetate, 4:1) to give aldehyde **3a** (19.9 g, 81% yield) as a yellow liquid.

Difluorovinylidenation of aldehydes (steps 3 and 4): The preparation of 1,1-difluoroallene **4a** is described as a typical procedure. To a THF solution (350 mL) of lithium diisopropylamide (LDA, 479 mmol), prepared from diisopropylamine (48.3 mL, 479 mmol) and *n*-butyllithium (1.60 M in hexanes, 300 mL, 480 mmol) at −78 °C for 30 min, was added 1,1,1-trifluoro-2-iodoethane (23.4 mL, 240 mmol) at −95 °C. After stirring for 30 min at −95 °C, a THF solution (300 mL) of aldehyde **3a** (368 mg, 200 mmol) was added. The mixture was stirred at −90 °C for 1 h and allowed to warm to −50 °C. Acetic anhydride (28.3 mL, 299 mmol) was added. After the mixture was allowed to warm to 0 °C and was stirred for 5 h, the reaction was quenched with saturated aqueous ammonium chloride (150 mL). The organic materials were extracted with EtOAc (3×100 mL). The combined extracts were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, crude 3,3-difluoro-2-iodoallyl acetate was obtained. This material was used without further purification for the next step.

To a DMF suspension (120 mL) of zinc powder (2.61 g, 399 mmol) was added a DMF solution (180 mL) of the crude acetate at −20 °C. After being stirred for 2 h at −20 °C, the mixture was allowed to warm to room temperature. The mixture was filtered through a pad of celite using diethyl ether as an eluent, and saturated aqueous ammonium chloride (100 mL) was added. The organic materials were extracted with diethyl ether (3×100 mL). The combined extracts were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue was subjected to column chromatography on silica gel (*n*-hexane) to give 1,1-difluoroallene **4a** (33.6 g, 73% yield, 2 steps) as a colorless liquid.

In^{III}-catalyzed cyclization of difluoroallenes (step 5): The synthesis of fluoroarene **1h** is described as a typical procedure. To a 1,2-dichloroethane suspension (4 mL) of indium(III) bromide (4 mg, 0.01 mmol) was added a 1,2-dichloroethane solution (10 mL) of 1,1-difluoroallene **4a** (120 mg, 0.523 mmol) at room temperature. After being stirred for 1 h, the mixture was then poured into pH 7 phosphate buffer (7 mL). The organic materials were extracted with CH_2Cl_2 (3×4 mL). The combined extracts were washed with brine and dried over anhydrous sodium sulfate. After removal of the solvent under reduced pressure, the residue was purified by column chromatography on silica gel (*n*-hexane) to give fluoroarene **1h** (103 mg, 94% yield) as colorless crystals.

Acknowledgements

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Keywords: aromatic substitution · fluorine · indium · microwave chemistry · ring extension

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COMMUNICATION

Aromatic Substitution

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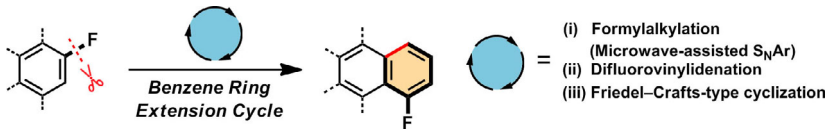
Synthesis of Pinpoint-Fluorinated Polycyclic Aromatic Hydrocarbons: Benzene Ring Extension Cycle Involving Microwave-Assisted S_NAr Reaction



Lords of the rings: Fluoroarenes bearing no electron-withdrawing groups (non-activated fluoroarenes) readily underwent nucleophilic aromatic substitution with α-cyanocarbanions under microwave irradiation. The sequence (i) formylalkylation involving cyanoalkylation of fluoroarenes, (ii) difluorovinylidenation, and (iii) Friedel–Crafts-type cyclization, afforded extended fluoroarenes by one benzene ring per cycle. Furthermore, the performance of multiple cycles successfully provided higher-order pinpoint-fluorinated polycyclic aromatic hydrocarbons (F-PAHs).