Grignard Cyclization Reaction of Fluorinated *N*-Arylimidoyl Chlorides: A Novel and Facile Access to 2-Fluoroalkyl Indoles

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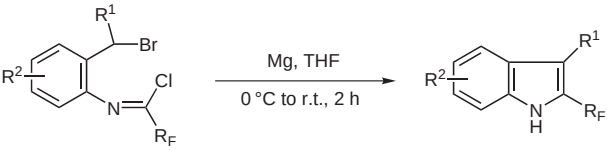
Abstract: 2-Fluoroalkyl-substituted indole derivatives were simply prepared via the Grignard cyclization reaction (GCR) of corresponding fluorinated *N*-aryl imidoyl chlorides in good yields. This approach provides a novel and facile access to the biologically important 2-fluoroalkylindole derivatives.

Key words: fluorine-containing Indoles, Grignard cyclizations, imidoyl chlorides, aryl amines, heterocycles

Due to the many potential bioactivities, fluorine-containing heterocycles have long received wide attention from either synthetic chemists or pharmaceutical scientists. As one of the important heterocycles, indole ring systems are found in many pharmaceuticals, for instance, indomethacin, oxypertine, and sumatriptan. Even today, the synthesis and applications of various indole derivatives are key subjects of considerable efforts.[1,2] However, indole ring systems bearing a fluoroalkyl group, especially 2- or 3-fluoroalkyl-substituted systems, have not been well-investigated due to the lack of efficient approaches to access the systems. Recently, Konno and his co-workers reported the palladium(0)-catalyzed regioselective annulation of fluorine-containing internal alkynes with *o*-iodoanilines, which provided a direct access to both 2- and 3-fluoroalkyl-substituted indole derivatives with good yields.[3] However, the application of this method is still somewhat limited due to the use of valuable palladium catalyst and the starting material source. Some other methods were also developed, but most of them suffered from either poor yields or the limitation of starting materials.[4] The development of novel and simple approach to synthesize the fluorine-containing indole derivatives from commercially or rapidly available materials still remains a challenge.

Our interest in the synthesis of 2-fluoroalkyl-substituted indoles arose from ongoing research projects for the synthesis of 2-trifluoromethyl-substituted indole 3-carbinol and indomethacin derivatives, which all contain the indole ring systems. In this letter, we wish to report and share our preliminary results from the synthesis of 2-fluoroalkyl indole derivatives via Grignard cyclization reaction (GCR) of the corresponding *N*-aryl imidoyl chlorides, which were readily prepared from commercially available *o*-alkylanilines and fluorine-containing carboxylic acids, This approach provides a novel and facile access to various 2-fluoroalkyl-subsituted indole derivatives specifically (Scheme 1).

The 2-fluoroalkyl-substituted indole derivatives **3** were successfully prepared through the GCR of either fluorinated *N*-(2-bromoalkyl)phenyl imidoyl chlorides **2** under normal Grignard reaction condition in moderate to good yields.[5]



2 **3**

R_F = CF_3, CF_2H, *n*-C_3F_7

Scheme 1 Grignard cyclization reaction (GCR) of *N*-aryl imidoyl chlorides

The yields of **3** from GCR of compounds **2** were found to be greatly affected by the electronic effect of the substituent group R^2 on the benzene ring. Without the substituent group (R^2 = H) or with an electron-donating group, such as methoxy, **3** could be obtained in good yields. With moderately electron-withdrawing groups, such as F, or Cl, the yields of **3** were decreased. While the presence of a strongly electron-withdrawing substituent, such as a nitro group, was found to inhibit the reaction and resulted in the total recovery of starting materials (Table 1). The process of this GCR was generally clean and no other by-products were in all cases examined. The high yielding and simple work-up procedure also enabled us to carry out the reactions even in larger scale.

The *N*-(2-bromoalkyl)phenyl imidoyl chlorides **2** were prepared simply, in two steps, from *o*-alkylanilines via an intermediate **1** according to Uneyama's one-pot approach.[6,7] Subsequent α-bromination at the benzylic position of compound **1** in the presence of *N*-bromosuccinimide (NBS)/benzoyl peroxide (BPO) resulted in the formation of *N*-[2-(bromoalkyl)phenyl]imidoyl chlorides **2** in good to excellent yields (Scheme 2).[8] Although *N*-[2-(bromoalkyl)phenyl]imidoyl chlorides **2** were generally

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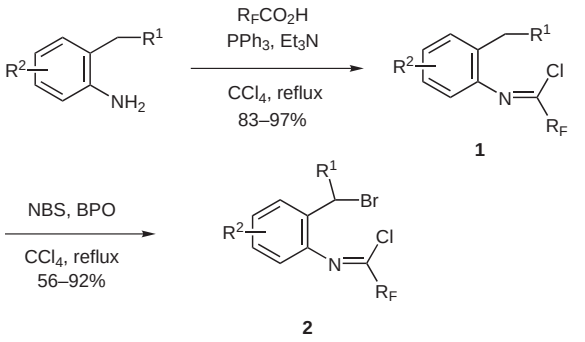
sensitive to acids, bases, and moisture, **2** can be purified by flash column chromatography on neutral or basic aluminum oxide, or by distillation under reduced pressure. Electron-withdrawing substituents such as a nitro group, substituted on the benzene ring, also decreased the yield of bromination reaction (entry 6, Table 1).



Scheme 2 Synthesis of *N*-[2-(bromoalkyl)phenyl]imidoyl chlorides

As described earlier, the 2-fluoroalkyl-substituted indole derivatives **3** could be efficiently synthesized via GCR from the corresponding fluorinated imidoyl chlorides **2** in good yields. As one application of this synthetic method, this approach provides us the possibility to explore the biological activities of such 2-fluoroalkyl-substituted new heteroauxin and indomethacin derivatives.

On the basis of this consideration, 3-methyl-2-trifluoromethylindole (**3b**) was selected as a substrate for the synthesis of 2-trifluoromethyl-substituted heteroauxin and indomethacin derivatives due to the easy modification of its 3-methyl group. Such modification could also lead to the formation of other interesting 3-substituted indole derivatives. Hence, protection of the amino group of **3b** with 4-chlorobenzoyl chloride[9] under basic conditions in DMSO–THF resulted in the formation compound **4** in 93% yield. Following bromination of 3-methyl group of **4** with NBS/AIBN in refluxing CCl_4 led to the formation of **5** in 85% yield (Scheme 3).[10] Nucleophilic substitution of **5** with NaCN was first examined in EtOH at room temperature, and resulted in the formation of N-deprotected nitrile **6** in 94% yield. This yield was obviously higher than those without 2-trifluoromethyl substituent because of the strong electron-withdrawing effect of the trifluoromethyl group. Under these reaction conditions, the nucleophilic cyanide anion attacked both the amide group and the bromide functionality. Subsequent hydrolysis of cyanide group of **6** led to the formation of 2-trifluoromethyl-substituted heteroauxin **7** in 62% yield,[11] which has the potential to be used as a new plant growth regulator or herbicide. The bioactivity of **7** is currently under investigation.

Alternatively, compound **7** was also a precursor for the synthesis of 2-trifluoromethyl-substituted indomethacin.

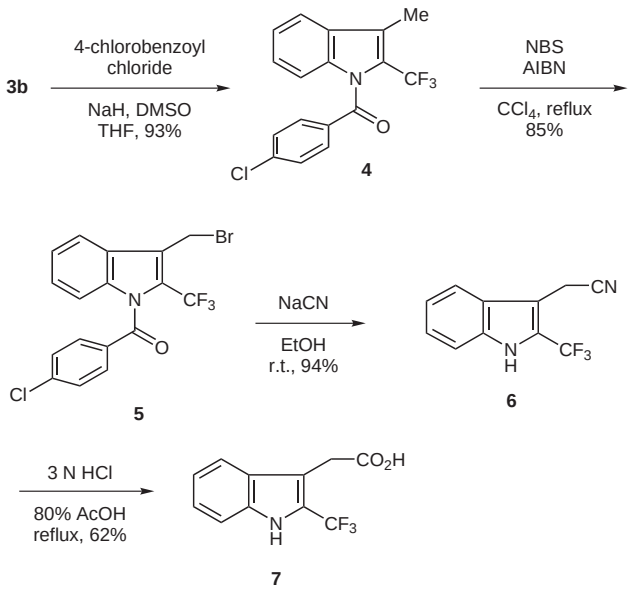
Hence, nucleophilic substitution reaction of **5** with malonate carbanion successfully led to the formation of compound **8** in 89% yield (Scheme 4).

In conclusion, a novel and facile approach for the synthesis of biologically important 2-fluoroalkyl-substituted indole derivatives via the GCR of the corresponding fluorinated imidoyl chlorides has been established. The nucleophilic substitutions of **5** have been demonstrated as one of the efficient ways to access new generation of interesting fluorine-containing indole derivatives, which may lead to the discovery of new and valuable biologically active molecules.

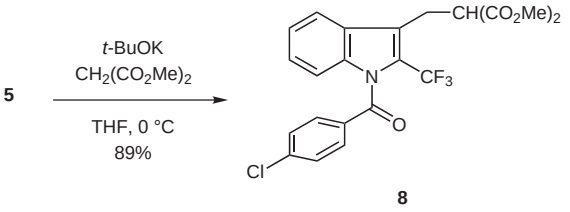
Table 1 Synthesis of 2-Fluoroalkyl-Substituted Indole Derivatives **3** from *o*-Alkylanilines

Entry	R_F	R^1	R^2	Yield of **1** (%)[a]	Yield of **2** (%)[a]	Yield of **3** (%)[a]
1	CF_3	H	H	**1a** 89	**2a** 91	**3a** 78
2	CF_3	Me	H	**1b** 86	**2b** 92	**3b** 82
3	CF_3	H	4-OMe	**1c** 92	**2c** 88	**3c** 75
4	CF_3	H	5-F	**1d** 97	**2d** 82	**3d** 62
5	CF_3	H	5-Cl	**1e** 97	**2e** 68	**3e** 45
6	CF_3	H	4-NO_2	**1f** 88	**2f** 56	–[b]
7	CF_2H	H	H	**1g** 83	**2g** 85	**3g** 77
8	CF_2H	H	4-OMe	**1h** 90	**2h** 82	**3h** 78
9	*n*-C_3F_7	Me	H	**1i** 89	**2i** 92	**3i** 79
10	*n*-C_3F_7	H	4-OMe	**1j** 90	**2j** 83	**3j** 76

[a] Isolated yields.
[b] Recovery of starting material.



Scheme 3 Synthesis of new trifluoromethyl-substituted hetero-auxin **7**



Scheme 4 Nucleophilic substitution of **5** with malonate carbanion

Acknowledgment

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(5) **General Procedure for the Synthesis of 2-Fluoroalkyl-Substituted Indoles 3.**
To a flame-dried 100 mL three-necked round-bottomed flask equipped with condenser and magnetic stir bar was added magnesium ribbon (0.3 g, 12.1 mmol) and anhydrous THF (25 mL) under a nitrogen atmosphere. A solution of the appropriate fluorinated *N*-[(2-bromoalkyl)phenyl]imidoyl chloride **2** (10.1 mmol) dissolved in THF (6 mL) was added dropwise at 0 °C. The reaction started within a few minutes. After addition, the reaction mixture was stirred for 2 h at 0 °C (monitored by TLC). Upon completion of the reaction, the reaction mixture was quenched with 10 mL sat. solution of NH_4Cl and extracted with EtOAc (15 mL, 3 ×). The combined organic layer was washed with brine, dried over Mg_2SO_4, and concentrated by rotary evaporator. The residue was then purified by column chromatography (20:1 hexane–EtOAc) on neutral Al_2O_3 to yield products **3**.
2-Trifluoromethylindole (3a).
Compound **3a** was obtained as a light yellow solid in 78% yield; mp 107–108 °C. ^{1}H NMR (500 MHz): δ = 8.30 (br, 1 H), 7.68 (d, *J* = 8.0 Hz, 1 H), 7.40 (d, *J* = 8.0 Hz, 1 H), 7.32 (t, *J* = 7.5 Hz, 1 H), 7.20 (t, *J* = 7.5 Hz, 1 H), 6.92 (s, 1 H). ^{13}C NMR (125 MHz): δ = 136.1, 126.6, 125.7 (q, $J_{C–C–F}$ = 38.8 Hz), 124.8, 122.1, 121.2 (q, $J_{C–F}$ = 266.2 Hz), 121.1, 111.7, 104.3 (q, $J_{C–C–C–F}$ = 3.3 Hz). ^{19}F NMR (470 MHz): δ = –60.50 (s, 3 F). IR (neat): 3389, 2921, 1375, 1306, 1196, 1168, 1103, 940, 818, 754 cm^{-1}. Anal. Calcd for $C_9H_6F_3N$: C, 58.38; H, 3.27; N, 7.57. Found: C, 58.39; H, 3.32; N, 7.55. HRMS: *m/z* calcd for $C_9H_6F_3N$ [M$^+$]: 185.0452; found: 185.0452.
3-Methyl-2-trifluoromethylindole (3b).
Compound **3b** was obtained as a yellow solid in 82% yield, using 1.5 equiv of magnesium ribbon; mp 73–74 °C. ^{1}H NMR (500 MHz): δ = 8.16 (br, 1 H) 7.64 (d, *J* = 8.0 Hz, 1 H), 7.38 (d, *J* = 8.5 Hz, 1 H), 7.32 (t, *J* = 7.7 Hz, 1 H), 7.19 (t, *J* = 7.5 Hz, 1 H), 2.44 (q, *J* = 1.7 Hz, 3 H). ^{13}C NMR (125 MHz): δ = 135.2, 128.1, 124.8, 122.1 (q, $J_{C–F}$ = 266.3 Hz), 121.6 (q, $J_{C–C–F}$ = 36.7 Hz), 120.4, 120.1, 114.1 (q, $J_{C–C–C–F}$ = 2.9 Hz), 111.6, 8.3. ^{19}F NMR (470 MHz): δ = –58.61 (s, 3 F). IR (neat): 3393, 2925, 1454, 1321, 1263, 1166, 1116, 756 cm^{-1}. HRMS: *m/z* calcd for $C_{10}H_8F_3N$ [M$^+$]: 199.0609; found: 199.0610.
5-Methoxy-2-trifluoromethylindole (3c).
Compound **3c** was obtained as a light yellow solid in 75% yield; mp 50–51 °C. ^{1}H NMR (500 MHz): δ = 8.30 (br, 1 H), 7.32 (d, *J* = 8.5 Hz, 1 H), 7.10 (d, *J* = 2.5 Hz, 1 H), 7.00 (dd, *J* = 9.0, 2.5 Hz, 1 H), 6.85 (s, 1 H), 3.86 (s, 3 H). ^{13}C NMR (125 MHz): δ = 154.8, 131.3, 127.1, 126.2 (q, $J_{C–C–F}$ = 38.4 Hz), 121.2 (q, $J_{C–F}$ = 265.9 Hz), 115.7, 112.6, 103.8 (q, $J_{C–C–C–F}$ = 3.3 Hz), 102.8, 55.7. ^{19}F NMR (470 MHz): δ = –60.45 (s, 3 F). IR (neat): 3402, 2949, 1559, 1461, 1384, 1224, 1174, 1117, 1023, 801 cm^{-1}. HRMS: *m/z* calcd for $C_{10}H_8F_3NO$ [M$^+$]: 215.0558; found: 215.0557.

6-Fluoro-2-trifluoromethylindole (3d).
Compound **3d** was obtained as a yellow viscous liquid in 62% yield; mp 126 °C (dec.). ^{1}H NMR (500 MHz): δ = 8.40 (br, 1 H), 7.58 (dd, *J* = 8.8, 5.2 Hz, 1 H), 7.06 (dd, *J* = 9.0, 1.8 Hz, 1 H), 6.96 (td, *J* = 9.0, 2.2 Hz, 1 H), 6.88 (s, 1 H). ^{13}C NMR (125 MHz): δ = 161.2 (d, $J_{C–F}$ = 240.0 Hz), 136.2 (d, $J_{C–C–C–F}$ = 12.5 Hz), 126.2 (q, $J_{C–C–F}$ = 39.2 Hz), 123.2 (d, $J_{C–C–C–F}$ = 10.0 Hz), 123.1, 121.0 (q, $J_{C–F}$ = 265.8 Hz), 110.4 (d, $J_{C–C–F}$ = 25.0 Hz), 104.4 (q, $J_{C–C–C–F}$ = 3.3 Hz), 97.9 (d, $J_{C–C–F}$ = 26.2 Hz). ^{19}F NMR (470 MHz): δ = –60.66 (s, 3 F), –116.7 (m, 1 F). IR (neat): 3463, 2929, 1567, 1323, 1258, 1174, 835 cm^{-1}. HRMS: *m/z* calcd for $C_9H_5F_4N$ [M$^+$]: 203.0358; found: 203.0361.

6-Chloro-2-trifluoromethylindole (3e).
Compound **3e** was obtained as a yellow viscous liquid in 45% yield, using 1.5 equiv of magnesium ribbon; mp 145 °C (dec.). ^{1}H NMR (500 MHz): δ = 8.41 (br, 1 H), 7.59 (d, *J* = 8.5 Hz, 1 H), 7.43–7.16 (m, 2 H), 6.91 (s, 1 H). ^{13}C NMR (125 MHz): δ = 136.4, 130.7, 126.4 (q, $J_{C–C–F}$ = 38.8 Hz), 125.1, 123.0, 122.1, 120.9 (q, $J_{C–F}$ = 266.3 Hz), 111.6, 104.3 (q, $J_{C–C–C–F}$ = 3.5 Hz). ^{19}F NMR (470 MHz): δ = –60.71 (s, 3 F). IR (neat): 3425, 2965, 1554, 1417, 1356, 1313, 1239, 1125, 922, 826 cm^{-1}. HRMS: *m/z* calcd for $C_9H_5ClF_3N$ [M$^+$]: 219.0063; found: 219.0059.

2-Difluoromethyl-5-methoxyindole (3h).
Compound **3h** was obtained as a yellow solid in 78% yield, using 1.5 equiv of magnesium ribbon; mp 76–78 °C. ^{1}H NMR (500 MHz): δ = 8.33 (br, 1 H), 7.24 (d, *J* = 9.0 Hz, 1 H), 7.08 (d, *J* = 2.5 Hz, 1H), 6.95 (dd, *J* = 9.0, 2.5 Hz, 1 H), 6.77 (t, $J_{H–F}$ = 55.0 Hz, 1 H), 6.66 (d, *J* = 2.0 Hz, 1 H), 3.84 (s, 3 H). ^{13}C NMR (125 MHz): δ = 154.6, 131.5, 130.6 (t, $J_{C–C–F}$ = 24.2 Hz), 127.4, 114.8, 112.4, 110.4 (t, $J_{C–F}$ = 233.8 Hz), 103.6 (t, $J_{C–C–C–F}$ = 6.8 Hz), 102.7, 55.7. ^{19}F NMR (470 MHz): δ = –109.8 (d, $J_{F–H}$ = 55.0 Hz, 2 F). IR (neat): 3459, 2959, 1561, 1456, 1372, 1206, 1173, 1134, 1070, 983, 809 cm^{-1}. HRMS: *m/z* calcd for $C_{10}H_9F_2NO$ [M$^+$]: 197.0652; found: 197.0654.

3-Methyl-2-perfluoropropylindole (3i).
Compound **3i** was obtained as a light yellow solid in 79% yield, using 1.5 equiv of magnesium ribbon; mp 73–75 °C. ^{1}H NMR (500 MHz): δ = 8.18 (br, 1 H), 7.67 (d, *J* = 8.0 Hz, 1 H), 7.41 (d, *J* = 8.0 Hz, 1 H), 7.35 (m, 1 H), 7.22 (m, 1 H), 2.45 (t, *J* = 2.2 Hz, 3 H). ^{13}C NMR (125 MHz): δ = 136.0, 128.3, 124.9, 120.4, 120.1, 119.3 (t, $J_{C–C–F}$ = 28.1 Hz), 118.0 (qt, $J_{C–F}$ = 286.2 Hz, $J_{C–C–F}$ = 33.8 Hz), 116.6 (t, $J_{C–C–C–F}$ = 3.8 Hz), 114.1 (tt, $J_{C–F}$ = 253.1 Hz, $J_{C–C–F}$ = 31.9 Hz), 111.5, 109.2 (m), 8.5 (q, *J* = 2.1 Hz). ^{19}F NMR (470 MHz): δ = –80.26 (t, *J* = 9.4 Hz, 3 F), –109.60 (q, *J* = 9.4 Hz, 2 F), –126.66 (s, 2 F). IR (neat): 3387, 2928, 1343, 1225, 1196, 1112, 903, 748 cm^{-1}. HRMS: *m/z* calcd for $C_{12}H_8F_7N$ [M$^+$]: 299.0545; found: 299.0548.

5-Methoxy-2-perfluoropropylindole (3j).
Compound **3j** was obtained as a light yellow solid in 76% yield, using 1.5 equiv of magnesium ribbon; mp 44–46 °C. ^{1}H NMR (500 MHz): δ = 8.54 (br, 1 H), 7.27 (d, *J* = 9.0 Hz, 1 H), 7.10 (d, *J* = 2.0 Hz, 1 H), 6.99 (dd, *J* = 8.8, 2.3 Hz, 1 H), 6.87 (s, 1 H), 3.84 (s, 3 H). ^{13}C NMR (125 MHz): δ = 155.0, 132.0, 127.5, 124.4 (t, $J_{C–C–F}$ = 29.4 Hz), 118.0 (qt, $J_{C–F}$ = 286.2 Hz, $J_{C–C–F}$ = 33.8 Hz), 116.1, 112.8 (tt, $J_{C–F}$ = 251.9 Hz, $J_{C–C–F}$ = 31.2 Hz), 112.7, 108.8 (m), 106.0 (t, *J* = 5.0 Hz), 102.7, 55.8. ^{19}F NMR (470 MHz): δ = –80.20 (t, *J* = 9.4 Hz, 3 F), –109.47 (q, *J* = 9.4 Hz, 2 F), –126.70 (s, 2 F). IR (neat): 3308, 2953, 1628, 1548, 1459, 1343, 1222, 1180, 976, 792 cm^{-1}. HRMS: *m/z* calcd for $C_{12}H_8F_7NO$ [M$^+$]: 315.0494; found: 315.0496.

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(7) **General Procedure for the Synthesis of Fluorinated *N*-(2-Alkylphenyl)Imidoyl Chlorides (1).**
To a 200 mL three-necked round-bottomed flask equipped with condenser and magnetic stir bar was added Ph_3P (34.5 g, 132 mmol), Et_3N(7.3 mL, 53 mmol), CCl_4 (21.1 mL, 220 mmol), and TFA, difluoroacetic acid or perfluorocarboxylic acid (44 mmol) at 0 °C under a nitrogen atmosphere and stirred for 10 min. A solution of *o*-alkylaniline (44 mmol) dissolved in CCl_4 (21.1 mL, 220 mmol) was added dropwise to the reaction mixture. Upon completion of the addition, the reaction mixture was allowed to reflux for 3 h. After cooling, the solvent was removed by rotary evaporator, the residue was then carefully washed with PE (3 ×), and the precipitation was removed via filtration. The filtrate was combined and concentrated by rotary evaporator. The residue was then purified by flash column chromatography (10:1 hexane–EtOAc) or distillation under reduced pressure to offer the products **1**.

(8) **General Procedure for the Synthesis of Fluorinated *N*-[(2-Bromoalkyl)phenyl]imidoyl Chlorides (2).**
To a 200 mL three-necked round-bottomed flask equipped with condenser and magnetic stir bar was added the appropriate fluorinated *N*-arylimidolyl chloride **1** (46 mmol), NBS (8.6 g, 48 mmol), benzoyl peroxide (0.6 g, 2.3 mmol), and anhydrous CCl_4 (80 mL) under a nitrogen atmosphere. This reaction mixture was stirred and heated to reflux for 2–5 h (monitored by TLC) until a complete conversion of **1**. After cooling down to r.t., the precipitate was removed via filtration. Then, the filtrate was combined and concentrated by rotary evaporator. The residue was then purified by flash column chromatography (10:1 hexane–EtOAc) or distillation under reduced pressure to yield products **2**.

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