A New and Efficient One-Pot Synthesis of 2-Fluoroalkyl Substituted Indoles

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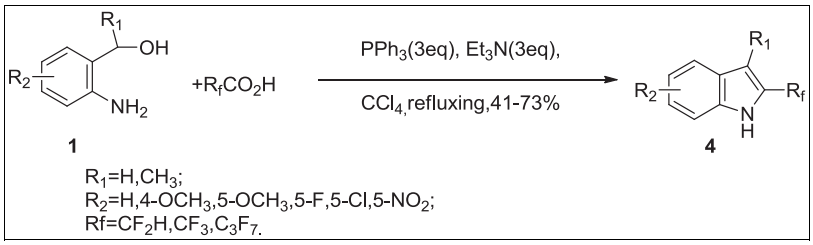

A new simple and efficient one-pot synthesis of 2-fluoroalkyl substituted indoles from 2-aminobenzyl alcohols with fluorine-containing carboxylic acids in the presence of Ph_3P, CCl_4, and NEt_3 is described. Various kinds of 2-fluoroalkyl substituted indole derivatives can be conveniently prepared.

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INTRODUCTION

Indoles and their derivatives are common heterocyclic compounds in nature. The indole ring system is an important structural component in many drugs [1]. The transition metal catalyzed ring closure methodology provides a direct access to the indole ring component with fewer steps and became a key strategy for the synthesis of indole ring system in last 40 years [2]. However, few synthetic methods provide efficient, scalable, and direct access to the biologically significant 2-fluoroalkyl substituted indoles. Therefore, the discovery of novel and facile routes to the construction of such a nitrogen-containing bicyclic system is still one of the important issues in organic synthesis.

RESULTS AND DISCUSSION

The synthetic strategy we disclose here is a one-pot cyclization of 2-aminobenzyl alcohols with fluorine-containing carboxylic acids in the presence of Ph_3P, CCl_4, and NEt_3. This process provides a convenient modular, scalable, and well-suited approach for the direct synthesis of various 2-fluoroalkyl substituted indole compounds in one step (Scheme 1).

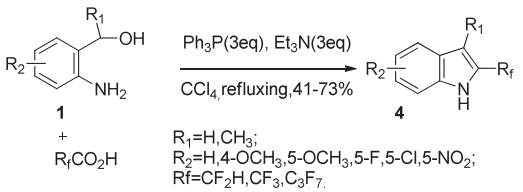
Prof. Hao and his team had reported the synthesis of 2-fluoroalkyl substituted indoles via the Grignard cyclization reaction of either fluorinated N-[2-(bromoalkyl)phenyl] imidoyl chlorides or N-[2-(chloroalkyl)phenyl]imidoyl chlorides with moderate to good yields [3]. They had also reported the synthesis of fluorine-containing benzoxazole [4] and indoline derivatives [5] from 2-aminophenol or 2-aminophenethyl alcohol via the Uneyama procedure [6], in this case, we wonder if we could obtain the fluoroalkyl-substituted benz-fused six-membered ring compound 2-(trifluoromethyl)-4H-benzo[d][1,3] oxazine **5** using 2-aminobenzyl alcohol via the aforementioned procedure, Instead, the cyclized 2-trifluoromethylindole **4a** was obtained in 55% yield (Scheme 2).

This unexpected result drew our attention to explore the mechanism of this one-pot cyclization process. It is clearly observed that during the model reaction with trifluoroacetic acid, the imidoyl chloride intermediate N-[2-(hydroxymethyl)phenyl]-2,2,2-trifluoroacetimidoyl chloride **2a** was formed at the initial stage, and with time going, **2a** disappeared gradually and instead the cyclized product **4a** was obtained as the final product. Decreasing the quantity of NEt_3 that was used in this reaction to one-third of normal dosage could effectively prevent the subsequential cyclization from being complete. Thus, the intermediate **2a** was successfully isolated as a major and stable compound from the reaction mixture. But the further cyclization of **2a** could be achieved only in the presence of Ph_3P, CCl_4, and NEt_3, which is different from the previous reports [4,5] (Scheme 3).

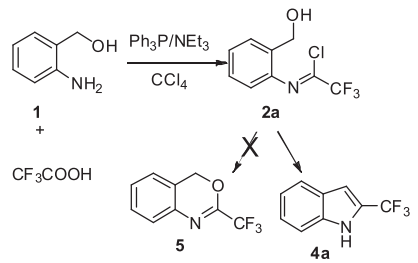
All imidoyl chloride intermediates, such as **2a**, were clearly detected in all examined cases and formed indole compounds except using 1-(2-aminophenyl)ethanol **1j** as the starting material, which formed N-(2-(1-chloroethyl) phenyl)-2,2,2-trifluoroacetimidoyl chloride **3j** instead of the corresponding indole compound (Scheme 4).

As we all known, $[Ph_3P^+Cl]\ CCl_3^-$ can be generated *in situ* from the reaction of Ph_3P with a large excess amount of CCl_4, which can convert the hydroxyl group to chlorine. N-[2-(hydroxymethyl)phenyl]-2,2,2-trifluoroacetimidoyl chloride **2a,** which could be detected formed N-[2-(hydroxymethyl)phenyl]-2,2,2-trifluoroacetimidoyl chloride **3a** firstly in the presence of Ph_3P, CCl_4, and NEt_3, So we supposed that

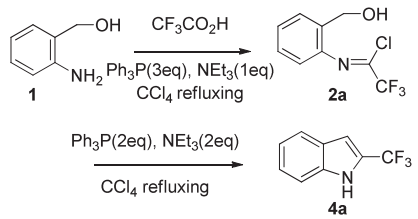
Scheme 1



Scheme 2



Scheme 3



Scheme 4

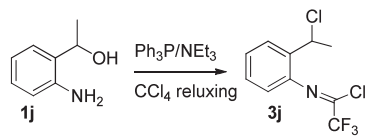


Table 1

Synthesis of various 2-fluoroalkyl substituted indole.

Entry	R_1	R_2	R_f	Yield of 4[a] (%)
1	H	H	CF_3	**4a** 55%
2	H	H	CF_2 H	**4b** 47%
3	H	H	C_3F_7	**4c** 62%
4	H	4-OCH_3	CF_3	**4d** 73%
5	H	4-F	CF_3	**4e** 55%
6	H	4-Cl	CF_3	**4f** 49%
7	H	4-NO2	CF_3	**4g** 41%
8	H	5-OCH_3	CF_3	**4h** 66%
9	H	5-OCH3	C_3F_7	**4i** 67%
10	CH_3	H	CF_3	**3j** 52%

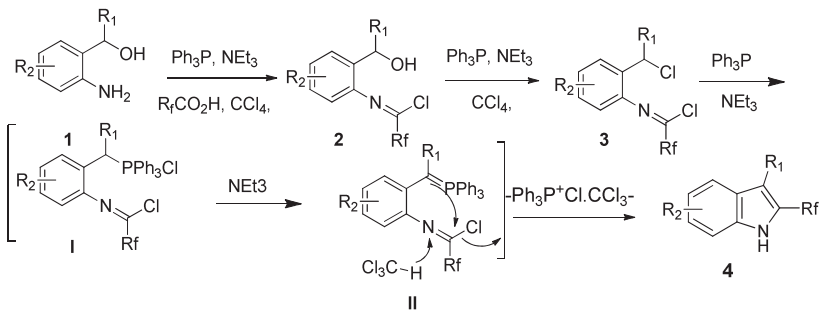
[a]The yields listed in this table are isolated yields.

Ph_3P attacked **3a** and formed a phosphonium salt **I** [7], the phosphonium salt **I** treated with NEt_3 and given a ylide **II,** which was very active and instable, once it formed, the subsequent cyclization could occur immediately and converted to **4** (Scheme 5). As **3j** is a secondary alkyl halide, the phosphonium salt intermediate **I** is hard to form, for this reason, we failed to obtain the corresponding indole.

This one-pot process is generally suitable to prepare various 2-fluoroalkyl substituted indoles with different fluorine-containing carboxylic acids and 2-aminobenzyl alcohols even in the hundreds of grams (Table 1). Most of the starting 2-aminobenzyl alcohols are commercially available, for specific structure demands, such as **1j**, the desired product can also be simply prepared by the reduction of 2-aminobenzoic acid or 2-nitrobenzoic acid [8].

It was found that the yields of **4** were affected by the electronic effects of substituent group R_2 on the benzene ring. Without substituent group ($R_2 = H$) or with electron-donating group, such as methoxyl group, the products are obtained in good yields, while with electron-deficient substituent, such as NO_2, the yields decreased to the moderate. When the substituent group at side-chain, such as ($R_1 = CH_3$), the reaction cannot occur.

Scheme 5



CONCLUSIONS

In conclusion, a unique and concise one-pot synthesis of 2-fluoroalkyl substituted indoles from of 2-aminobenzyl alcohols, and fluorine-containing carboxylic acids has been developed. This new approach provides an efficient, scalable, low-cost, and direct access to the biologically important indoles.

EXPERIMENTAL

General. All melting points were taken on a WRS-1A or WRS-1B Digital Melting Point Apparatus without correction. ^{1}H-NMR, ^{13}C-NMR, and ^{19}F-NMR spectra were recorded in $CDCl_3$ on a Bruker AV-500 spectrometer. Chemical shifts for ^{1}H-NMR spectra are reported in ppm downfield from TMS, chemical shifts for ^{13}C-NMR spectra are reported in ppm relative to internal chloroform (δ 77.0 ppm for ^{13}C), and chemical shifts for ^{19}F-NMR spectra are reported in ppm downfield from external fluorotrichloro-methane ($CFCl_3$). Coupling constants (*J*) are given in Hertz (Hz). The terms m, s, d, t, and q refer to multiplet, singlet, doublet, triplet, and quartet; br refers to a broad signal. Infrared spectra (IR) were recorded on AVATAR 370 FT-IR spectrometer. Elemental analyses were carried out on a VARIO EL111 elemental analyzer.

General procedure. To a 100-mL three-necked round-bottomed flask equipped with a condenser and a magnetic stir bar was added Ph_3P (7.86 g, 30 mmol), NEt_3 (4.2 mL, 30 mmol), CCl_4 (40 mL, 419 mmol), and carboxylic acid (10 mmol) at 0°C under nitrogen atmosphere and the solution was then stirred for 10 min, following 2-aminobenzyl alcohols **1** (10 mmol) was added to the reaction mixture. Once the addition was completed, the reaction mixture was allowed to reflux for 3–12 h_k;. After cooling, the solvent was removed by rotary evaporator, the residue was then carefully washed with mixture solvent (4:1 hexane:ethyl acetate) three times, and the precipitate was removed via filtration. The filtrate was combined and concentrated by rotary evaporator. The residue was then purified by column chromatography to offer the product **4a–4i** and **3j**.

Characterizations of products.

2-Trifluoromethylindole (4a). In 55% yield, **4a** was obtained as a light yellow solid by column chromatography (4:1 hexane:ethyl acetate) on neutral aluminum oxide: mp 107–108°C; ^{1}H-NMR (500 MHz) δ 8.31 (br, 1H, N*H*), 7.66 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 6.92 (s, 1H); ^{13}C-NMR (125 MHz) δ 136.1, 126.5, 125.7 (q, $^{2}J_{C-F}$ = 38.8 Hz, *C*-CF_3), 124.7, 121.9, 121.2 (q, $^{1}J_{C-F}$ = 266.2 Hz, *C*F_3), 121.1, 111.7, 104.3 (q, $^{3}J_{C-F}$ = 3.3 Hz, *C*H = C-CF_3); ^{19}F-NMR (470 MHz) δ −60.50 (s, 3 F); IR (neat) 3389 (NH), 2921, 1375, 1306, 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, 58.40; H, 3.31; N, 7.55.

2-Difluoromethylindole (4b). In 47% yield, **4b** was obtained as a yellow solid: mp 56–58°C; ^{1}H-NMR (500 MHz) δ 8.31 (br, 1H, N*H*), 7.65 (d, *J* = 8.0 Hz, 1H, Ar-*H*), 7.35 (d, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.17 (t, *J* = 7.5 Hz, 1H), 6.81 (t, J_{H-F} = 54.5 Hz, 1H, CF_2H), 6.74 (d, J_{H-F} = 2.0 Hz, 1H, C*H* = C-CF_2H); ^{13}C-NMR (125 MHz) δ 136.2, 130.0 (t, $^{2}J_{C-F}$ = 24.2 Hz, *C*-CF_2H), 126.9, 124.1, 121.6, 120.6, 111.6, 110.5 (t, $^{1}J_{C-F}$ = 233.4 Hz, *C*F_2H), 103.9 (t, $^{3}J_{C-F}$ = 6.9 Hz, *C*H = C-CF_2H); ^{19}F-NMR (470 MHz) δ −109.83 (d, J_{F-H} = 54.9 Hz, 2 F); IR (neat) 3395 (NH), 2924, 1621, 1371, 1069, 1015, 810, 750 cm^{-1}; *Anal.* Calcd for $C_9H_7F_2N$: C, 64.67; H, 4.22; N, 8.38. Found: C, 64.66; H, 4.19; N, 8.35.

2-Heptafluoropropylindole (4c). In 62% yield, **4c** was obtained as a light yellow solid: mp 63–64°C; ^{1}H-NMR (500 MHz) δ 8.32 (br, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.37 (d, *J* = 8.0 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.16 (t, *J* = 7.5 Hz, 1H), 6.87 (s, 1H); ^{13}C-NMR (125 MHz) δ 136.1, 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),124.1,121.1, 117.7, 112.8 (tt, J_{C-F} = 251.9 Hz, J_{C-C-F} = 31.2 Hz), 111.7,108.8 (m), 106.0 (t, *J* = 5.0 Hz); ^{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, 1232, 1080, 814, 760 cm^{-1}; *Anal.* Calcd for $C_{11}H_6F_7N$: C, 46.33; H, 2.12; N, 4.91. Found: C, 46.36; H, 2.09; N, 4.85.

6-Methoxy-2-trifluoromethyl indole (4d). In 73% yield, **4d** was obtained as a colorless solid: mp 88–90°C; ^{1}H-NMR (500 MHz) δ 8.28 (br, 1H, N*H*), 7.48 (d, *J* = 8.5 Hz, 1H), 7.10 (d, *J* = 2.5 Hz, 1H), 6.89 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.86 (s, 1H, C*H* = C-CF_3), 3.85 (s, 3H); ^{13}C-NMR (125 MHz) δ 158.2, 137.3, 126.2 (q, $^{2}J_{C-F}$ = 38.4 Hz, *C*-CF_3), 122.7, 121.2 (q, $^{1}J_{C-F}$ = 265.9 Hz, *C*F_3), 119.7, 111.6, 104.3 (q, $^{3}J_{C-F}$ = 3.3 Hz, *C*H = C-CF_3), 94.8, 55.7 (Ar-O*C*H_3); ^{19}F-NMR (470 MHz) δ −60.45 (s, 3 F); IR (neat) 3302 (NH), 2959, 1599, 1560, 1254, 1174, 1117, 1001 cm^{-1}; *Anal.* Calcd for $C_{10}H_8F_3NO$: C, 55.82; H, 3.75; N, 6.51; O, 7.44. Found: C, 55.86; H, 3.77; N, 6.45; O, 7.46.

6-Fluoro-2-trifluoromethylindole (4e). In 55% yield, **4e** was obtained as a yellow viscous liquid: mp 125°C (dec.); ^{1}H-NMR (500 MHz) δ 8.38 (br, 1H, N*H*), 7.57 (dd, *J* = 8.8, 5.2 Hz, 1H), 7.06 (m, 1H), 6.96 (m, 1H), 6.88 (s, 1H, C*H* = C-CF_3); ^{13}C-NMR (125 MHz) δ 161.1 (d, $^{1}J_{C-F}$ = 240.0 Hz), 136.2 (d, $^{3}J_{C-F}$ = 12.5 Hz), 126.2 (q, $^{2}J_{C-F}$ = 39.2 Hz, *C*-CF_3), 123.2 (d, $^{3}J_{C-F}$ = 10.0 Hz), 122.9, 121.1(q, $^{1}J_{C-F}$ = 265.8 Hz, *C*F_3), 110.2 (d, $^{2}J_{C-F}$ = 25.0 Hz), 104.3 (q, $^{3}J_{C-F}$ = 3.3 Hz, *C*H = C-CF_3), 97.8 (d, $^{2}J_{C-F}$ = 26.2 Hz); ^{19}F-NMR (470 MHz) δ −60.56 (s, 3 F, C*F*$_3$), −116.7 (m, 1 F, Ar-*F*); IR (neat) 3457 (NH), 2938, 1566, 1305, 1249, 1169, 831 cm^{-1}; *Anal.* Calcd for $C_9H_5F_4N$: C, 53.21; H, 2.48; N, 6.90. Found: C, 53. 17; H, 2.50; N, 6.91.

6-Chloro-2-trifluoromethylindole (4f). In 49% yield, **4f** was obtained as a yellow viscous liquid: mp 147°C (dec.); ^{1}H-NMR (500 MHz) δ 8.40(br, 1H, N*H*), 7.56 (d, *J* = 8.5 Hz, 1H), 7.43–7.16 (m, 2H, Ar-*H*), 6.91 (s, 1H, C*H* = C-CF_3); ^{13}C-NMR (125 MHz) δ 136.3, 130.8, 126.2 (q, $^{2}J_{C-F}$ = 38.8 Hz, *C*-CF_3), 124.8, 122.7, 122.1, 120.6 (q, $^{1}J_{C-F}$ = 266.3 Hz, *C*F_3), 111.5, 103.8 (q, $^{3}J_{C-F}$ = 3.5 Hz, *C*H = C-CF_3); ^{19}F-NMR (470 MHz) δ −60.61 (s, 3 F); IR (neat) 3425 (NH), 1554, 1416, 1357, 1310, 1125, 922, 826 cm^{-1}; *Anal.* Calcd for $C_9H_5ClF_3N$: C, 49.23; H, 2.30; N, 6.38. Found: C, 49.35; H, 2.28; N, 6.40.

6-Nitro-2-trifluoromethylindole (4g). In 41% yield, **4g** was obtained as a yellow solid: mp 143–144°C; ^{1}H-NMR (500 MHz) δ 8.45(br, 1H, N*H*), 8.26 (d, *J* = 8.5 Hz, 1H), 7.50–7.55 (m, 2H), 6.95 (s, 1H, C*H* = C-CF_3); ^{13}C-NMR (125 MHz) δ 140.3, 138.8, 127.9 (q, $^{2}J_{C-F}$ = 38.6Hz, *C*-CF_3), 123.7 122.7, 122.1, 120.8 (q, $^{1}J_{C-F}$ = 266.3 Hz, *C*F_3), 118.5, 102.4 (q, $^{3}J_{C-F}$ = 3.5 Hz, *C*H = C-CF_3); ^{19}F-NMR (470 MHz) δ −60.81 (s, 3 F); IR (neat) 3380 (NH), 1654, 1515, 1456, 1300, 1025, 927, 835 cm^{-1}; *Anal.* Calcd for $C_9H_5F_3N_2O_2$: C, 46.97; H, 2.19; N, 12.17; O, 13.90. Found: C, 46.92; H, 2.17; N, 12.18; O, 13.93.

5-Methoxy-2-trifluoromethyl indole (4h). In 66% yield, **4h** was obtained as a light yellow solid: mp 50–51°C; ^{1}H-NMR (500 MHz) δ 8.30 (br, 1H, N*H*), 7.33 (d, *J* = 8.5 Hz, 1H), 7.11 (d, *J* = 2.5 Hz, 1H), 7.00 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.84 (s, 1H, C*H* = C-CF_3), 3.86 (s, 3H, Ar-OC*H*$_3$); ^{13}C-NMR (125 MHz) δ 154.7, 131.3, 127.1, 126.2 (q, $^2J_{C-F}$ = 38.4 Hz, *C*-CF_3), 121.2 (q, $^1J_{C-F}$ = 265.9 Hz, *C*F_3), 115.6, 112.4, 103.8 (q, $^3J_{C-F}$ = 3.3 Hz, *C*H = C-CF_3), 102.7, 55.5 (Ar-OCH_3); ^{19}F-NMR (470 MHz) δ −60.45 (s, 3 F); IR (neat) 3402 (NH), 2949, 1559, 1461, 1224, 1174, 1117, 801 cm^{-1}; *Anal.* Calcd for $C_{10}H_8F_3NO$: C, 55.82; H, 3.75; N, 6.51; O, 7.44. Found: C, 55.85; H, 3.76; N, 6.48; O, 7.56.

5-Methoxy-2-heptafluoropropylindole (4i). In 67% yield, **4i** was obtained as a light yellow solid: mp 44–45°C; ^{1}H-NMR (500 MHz) δ 8.52 (br, 1H, N*H*), 7.27 (d, *J* = 9.0 Hz, 1H), 7.10 (d, *J* = 2.0 Hz, 1H), 7.01 (dd, *J* = 8.8, 2.3 Hz, 1H), 6.87 (s, 1H, C*H* = C-C_3F_7), 3.84 (s, 3H); ^{13}C-NMR (125 MHz) δ 155.1, 132.0, 127.5, 124.3 (t, $^2J_{C-F}$ = 29.4 Hz, *C*-C_3F_7), 118.0 (qt, $^1J_{C-F}$ = 286.2 Hz, $^2J_{C-F}$ = 33.8 Hz, $CF_2CF_2CF_3$), 116.1, 112.8 (tt, $^1J_{C-F}$ = 251.9 Hz, $^2J_{C-F}$ = 31.2 Hz, $CF_2CF_2CF_3$), 112.7, 108.8 (m, CF_2CF_2-CF_3), 106.0 (t, ^3J = 5.0 Hz, *C*H = C-C_3F_7), 102.7, 55.8 (Ar-OCH_3); ^{19}F-NMR (470 MHz) δ −80.20 (t, *J* = 9.4 Hz, 3 F, $CF_2CF_2CF_3$), −109.47 (q, *J* = 9.4 Hz, 2 F, $CF_2CF_2CF_3$), −126.70 (s, 2 F, $CF_2CF_2CF_3$); IR (neat) 3318 (NH), 2956, 1545, 1450, 1345, 1232, 1181, 967, 790 cm^{-1}; *Anal.* Calcd for $C_{12}H_8F_7NO$: C, 45.73; H, 2.56; N, 4.44; O, 5.08. Found: C, 45.75; H, 2. 60; N, 4.42; O, 5.11.

N-[2-(1-Chloroethyl)phenyl]-2,2,2-trifluoroacetimidoyl chloride (3j). In 52% yield, **3j** was obtained as a colorless oil by flash column chromatography on neutral Al_2O_3: bp 80–82°C/9 mmHg; ^{1}H-NMR (500 MHz) δ 7.65 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.40–7.31 (m, 2H, Ar-*H*), 6.95 (dd, *J* = 7.5, 1.2 Hz, 1H), 5.45 (q, *J* = 7.0 Hz, 1H), 2.15 (d, *J* = 7.0 Hz, 3H); ^{13}C-NMR (125 MHz) δ 141.1, 134.9, 134.2 (q, $^2J_{C-F}$ = 42.9 Hz, *C*-CF_3), 128.8, 127.7, 126.5, 119.2, 116.7 (q, $^1J_{C-F}$ = 275.8 Hz, *C*F_3), 56.4, 26.1; ^{19}F-NMR (470 MHz) δ −71.60 (s, 3 F); IR (neat) 2980, 1697 (C=N), 1486, 1288, 1209, 1165, 951, 765 cm^{-1}; *Anal.* Calcd for $C_{10}H_8Cl_2F_3N$: C, 44.47; H, 2.99; N, 5.19. Found: C, 44.50; H, 3.01; N, 5.21.

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