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Synthesis of mono- and difluorobenzyl chlorides by chlorination of mono- and difluorotoluenes with CCl_4 and *t*-BuOCl induced by iron-containing catalysts

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ABSTRACT

Mono- and difluorobenzyl chlorides were synthesized by chlorination of mono- and difluorotoluenes with CCl_4 – MeOH or *t*-BuOCl in the presence of iron-containing catalysts.

1. Introduction

Selective chlorination of the C(sp^3)–H-group of toluene and its substituted derivatives is one of the important problems of organic synthesis. For the chlorination of the methyl group of toluene in order to obtain benzyl chloride, various reagents are used. They are Cl_2 [1], SO_2Cl_2 [2,3], *N*-chlorosuccinimide [4], *t*-BuOCl [5], $PhICl_2$ [6], trichloroisocyanuric acid [7,8], NaCl/HCl – *hv* [9,10], NaCl or KCl/Oxone [11,12].

Among benzyl chlorides, mono- and difluorobenzyl chlorides are of particular interest, the main scope of which is the synthesis of pharmaceutical drugs [13,14]. Indeed, *p*-fluorobenzyl chloride serves as the starting compound for the preparation of 2-(4-fluorobenzyl)thiophene, which is, in turn, the key intermediate in the synthesis of the ABT-761 drug [15]. 2,6-Difluorobenzyl chloride is the precursor of rufinamide, a known drug with an antiepileptic action [16].

Isomeric (di)fluorobenzyl chlorides are prepared in 60–93% yields by photochlorination of appropriate (di)fluorotoluenes with molecular chlorine at elevated temperature of 70–180 °C [17–19].

o-, *m*-, and *p*-Fluorobenzyl chlorides are formed in 70–75% yields upon chlorination of the corresponding fluorotoluenes with sulfuryl chloride in the presence of the PCl_3 catalyst under UV irradiation [20].

A high yield of *p*-fluorobenzyl chloride (79%) was observed in the chlorination of *p*-fluorotoluene with *N*-chlorosuccinimide in the presence of initiators of radical reactions such as *N*-hydroxyphthalimide and 2,3-dicyano-5,6-dichlorobenzoquinone [4]. Photocatalytic chlorination of *p*-fluorotoluene with NaCl/HCl in the presence of silver nanoparticles and AgCl has been reported by the authors of the work [9].

Trichloroisocyanuric acid was found to promote photocatalytic chlorination of *p*-fluorotoluene at the methyl group under mild reaction conditions (r.t., 8 h) [8].

The purpose of this study was to develop a new synthetic route to mono- and difluorobenzyl chlorides via chlorination of (di)fluorotoluenes using tetrachloromethane and *tert*-butyl hypochlorite in the presence of Fe catalysts.

2. Results and discussion

In this study, mono- and difluorobenzyl chlorides were synthesized by the reaction of *o*-, *m*-, and *p*-fluoro- and 2,4-, 2,5-, and 2,6-difluorotoluenes with CCl_4 with the following iron compounds and complexes as catalysts: $FeCl_3$, $FeBr_2$, $FeCl_2{\cdot}4H_2O$, $Fe_2(CO)_9$, and Fe$(C_5H_5)_2$, in the presence of methanol. The best results were obtained using $FeCl_2{\cdot}4H_2O$ and $FeBr_2$ catalysts, with addition of amides, among which formamide was the compound of choice (Table 1).

Subsequently, we used available formamide as the promotory additive for the synthesis of mono- and difluorobenzyl chlorides.

The experiments were performed at various reactant and catalyst concentrations. The conditions of choice are as follows: 180 °C, 6 h, and the catalyst and reactant molar ratios of [Fe]:[$HCONH_2$]:[*o*-, *m*-, *p*-fluorotoluene (**1–3**)]:[CCl_4]:[MeOH] = 1:50:100:200:50. The yields of *o*-, *m*-, and *p*-fluorobenzyl chlorides (**1a-3a**) were 11–67% (Table 2). The experiments were conducted in an argon atmosphere. In the absence of the catalyst and the alcohol, the reaction did not take place.

Subsequently, we attempted to chlorinate 2,4-, 2,5-, and 2,6-difluorotoluenes (**4–6**). As shown by experiments, $FeCl_2{\cdot}4H_2O$–$HCONH_2$

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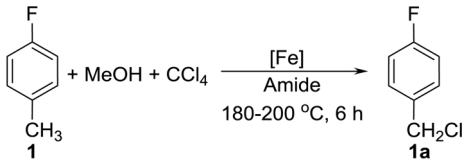
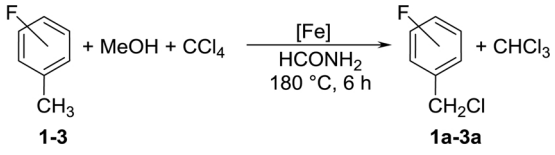
Table 1
Reaction of *p*-fluorotoluene **1** with CCl_4 and MeOH catalyzed by iron compounds in the presence of amides.



[Fe]: [Amide]: [**1**]: [CCl_4]: [MeOH] = 1: 50: 100: 200: 50

Entry	Catalyst	Amide	T, °C	Conversion of **1**, %	Yield of **1a**, %
1	$FeCl_3$	$HCONH_2$	180	43	42
2	$Fe_2(CO)_9$	$HCONH_2$	180	45	42
3	$Fe(C_5H_5)_2$	$HCONH_2$	180	61	30
4	$FeBr_2$	$HCONH_2$	180 (200)	68 (70)	58 (61)
5	$FeCl_2{\cdot}4H_2O$	$HCONH_2$	180 (200)	68 (73)	67 (70)
6	$FeBr_2$	$EtCONH_2$	180 (200)	32 (45)	29 (38)
7	$FeBr_2$	$MeCONH_2$	180 (200)	23 (42)	21 (39)
8	$FeBr_2$	$PhCONH_2$	180 (200)	25 (52)	21 (48)
9	$FeBr_2$	$H_2N\text{-}CO\text{-}NH_2$	180 (200)	21 (30)	17 (19)
10	$FeBr_2$	$(CH_3)_2NCOCH_3$	180 (200)	19 (25)	13 (24)
11	$FeCl_2{\cdot}4H_2O$	$EtCONH_2$	180 (200)	45 (58)	30 (54)
12	$FeCl_2{\cdot}4H_2O$	$MeCONH_2$	180 (200)	33 (49)	29 (47)
13	$FeCl_2{\cdot}4H_2O$	$PhCONH_2$	180 (200)	37 (54)	24 (36)
14	$FeCl_2{\cdot}4H_2O$	$H_2N\text{-}CO\text{-}NH_2$	180 (200)	30 (32)	23 (30)
15	$FeCl_2{\cdot}4H_2O$	$(CH_3)_2NCOCH_3$	180 (200)	22 (25)	22 (23)

Table 2
Reactions of *o*-, *m*-, and *p*-fluorotoluenes **1–3** with MeOH and CCl_4 in the presence of $FeCl_2{\cdot}4H_2O$–$HCONH_2$ and $FeBr_2$–$HCONH_2$ catalytic systems.



[Fe]: [$HCONH_2$]: [***1-3***]: [CCl_4]: [MeOH] = 1: 50: 100: 200: 50
[Fe] = $FeBr_2$, $FeCl_2{\cdot}4H_2O$

Catalyst	Fluorotoluene **1-3**	Conversion of **1-3**, %	Yield of **1a-3a**, %
$FeCl_2{\cdot}4H_2O$	*p*-Fluorotoluene **1**	68	67
$FeCl_2{\cdot}4H_2O$	*m*-Fluorotoluene **2**	35	35
$FeCl_2{\cdot}4H_2O$	*o*-Fluorotoluene **3**	30	30
$FeBr_2$	*p*-Fluorotoluene **1**	68	58
$FeBr_2$	*m*-Fluorotoluene **2**	11	11
$FeBr_2$	*o*-Fluorotoluene **3**	15	15

and $FeBr_2$–$HCONH_2$ are those catalytic systems which catalyze chlorination of **4–6** to give reasonable yields of difluorobenzyl chlorides (**4a-6a**). In particular, in the presence of the $FeCl_2{\cdot}4H_2O$–$HCONH_2$ system, the conversion of difluorotoluenes was 27–47%, with high selectivity towards difluorobenzyl chlorides being retained (Scheme 1).

To find the causes behind the favorable effect of the alcohol on the reaction performance and considering the known fact of formation of methyl hypochlorite upon the reaction of CCl_4 with methanol in the presence of transition metal complexes [21], we analyzed the reaction mixture for the content of "active chlorine". This was done using the $FeBr_2$-catalyzed reaction of fluorotoluene with CCl_4 and methanol in the presence of formamide. According to iodometric titration data, the concentration of "active chlorine" in experiments varied from 1.1 to 1.5 mg/mL. This suggests the possibility of formation of methyl hypochlorite (Scheme 2) upon the reaction of MeOH with CCl_4, acting as a chlorinating agent or the initiator of radical chlorination with CCl_4. Methyl hypochlorite is relatively unstable and readily decomposes to give off CH_2O and HCl; therefore, for the reaction to proceed smoothly, an excess of methanol is required.

According to the results of titration, the reaction mixture contained ammonium ions (Scheme 2), the concentration of which in the experiments varied from 17.8 mg/mL to 25.79 mg/mL (Table 3). It is evident that ammonia needed for binding of HCl is formed upon formamide decomposition, which is facilitated by elevated temperature (180 °C). Thus, amides act as acceptors of HCl evolved upon MeOCl decomposition.

When no amide is present in the catalyst, along with *p*-fluorobenzyl chloride **1a**, the reaction gives difluoroaryl methanes as side products, mainly 1-fluoro-2-(4-fluorobenzyl)-4-methylbenzene (**1b**) and 4-fluoro-2-(4-fluorobenzyl)-1-methylbenzene (**1c**) (2:1) (Scheme 3).

It is noteworthy that the highest promoting effect on the reaction is inherent in methanol: in the presence of other alcohols (EtOH, *n*-PrOH), the yields of mono- and difluorobenzyl chlorides were three times lower. It is impossible to separately evaluate the contributions of CCl_4 and MeOCl as chlorinating agents, as chlorination with CCl_4 is also accompanied by chloroform formation.

Therefore, in order to verify the assumption that methyl hypochlorite, which is generated from CCl_4 and methanol under the action of the catalyst, is involved in chlorination of fluorotoluenes, we attempted the chlorination of *p*-fluorotoluene **1** with stable *tert*-butyl hypochlorite (*t*-BuOCl).

As shown by experiments, the course of chlorination of *p*-fluorotoluene **1** with *t*-BuOCl is considerably affected by the catalyst. Under chosen reaction conditions (20 °C, 3 h), the conversion of *p*-fluorotoluene **1** in the reaction with *t*-BuOCl (3 equiv.) without a catalyst was 8% (Table 4, entry 4), while in the presence of the $FeCl_2{\cdot}4H_2O$ catalyst (1 mol%), the conversion of *p*-fluorotoluene **1** reached 70% and the yield of **1a** was 65% (Table 4, entry 2). The yield of **1a** was decreased to 56% when 1 equiv. of *t*-BuOCl was used (Table 4, entry 1). The second reaction product was *t*-BuOH, which was formed in a stoichiometric amount.

It is noteworthy that chlorination of *p*-fluorotoluene **1** with *t*-BuOCl does not require formamide as a part of the catalytic system since no HCl is present.

A similar chlorination with *t*-BuOCl in the presence of iron-containing catalysts can be carried out for *o*- and *m*-fluorotoluenes and for 2,4-, 2,5-, and 2,6-difluorotoluenes **2-6**. The yields of the corresponding mono- and difluorobenzyl chlorides **2a-6a** are 24–65% (Table 5).

The role of the iron-containing catalyst is probably to cleave *t*-BuOCl generating the *t*-BuO· and Cl· radicals, which then react with fluorotoluenes at the methyl group.

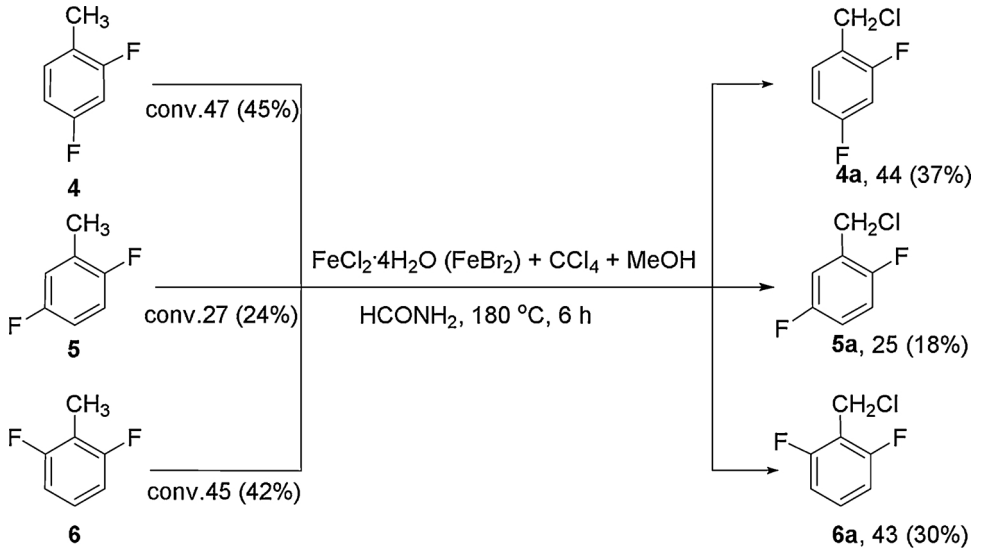
The structures of the obtained fluorobenzyl chlorides were reliably proven by ^1H, ^{13}C, and ^{19}F NMR data.

The presence of the CH_2Cl group in compounds **1a-3a** was evidenced by a characteristic carbon ^{13}C NMR signal at δ 39.5–45.5 ppm and the singlet signal for the CH_2 protons at 4.6–4.7 ppm. Furthermore, the ^{19}F NMR spectra unambiguously indicate that the fluorine atoms resonating at –113.2 ppm (*p*-fluorobenzyl chloride **1a**), –112.5 ppm (*m*-fluorobenzyl chloride **2a**), and –117.7 ppm (*o*-fluorobenzyl chloride **3a**) are attached to the aromatic ring. This is confirmed by the characteristic signal splitting of sp^2-hybridized carbon atoms in ^{13}C NMR spectra.

The ^{13}C NMR spectra of 2,4-, 2,5-, and 2,6-difluorobenzyl chlorides **4a-6a** are more complex, since each aromatic carbon atom gives rise to a multiplet as a result of splitting due to the spin-spin interactions (with several coupling constants ($^nJ_{C,\ F}$)).

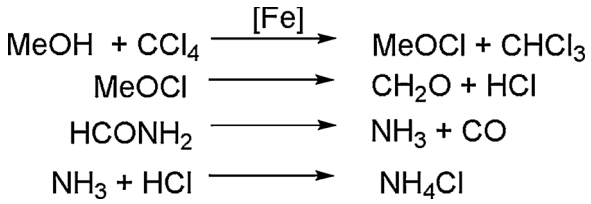
3. Conclusions

We have implemented selective chlorination of mono- and difluorotoluenes with tetrachloromethane and methanol (180–200 °C, 6 h) at the CH_3-group under the action of [Fe]–$RCONH_2$ catalyst to produce mono- and difluorobenzyl chlorides with yield up to 70%. The



$[FeCl_2{\cdot}4H_2O\ (FeBr_2)]$: $[HCONH_2]$: **[4-6]**: $[CCl_4]$: $[CH_3OH]$ = 1: 50: 100: 200: 50

Scheme 1. Synthesis of difluorobenzyl chlorides **4a-6a** by the reaction of difluorotoluenes **4–6** with CCl_4 and MeOH in the presence of the $FeCl_2{\cdot}4H_2O$ ($FeBr_2$) – $HCONH_2$ catalytic system.



Scheme 2. Formation of methyl hypochlorite and the ammonium ion.

Table 3
Concentration of ammonium ions [NH_4^+] (mg/mL) in the reaction of *p*-fluorotoluene **1** with MeOH and CCl_4 in the presence of [Fe] – $RCONH_2$.[a].

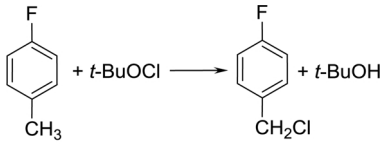
Entry	Catalyst	$RCONH_2$	[NH_4^+], mg/mL
1	$FeCl_2{\cdot}4H_2O$	$HCONH_2$	19.7
2	$FeCl_2{\cdot}4H_2O$	$EtCONH_2$	24.2
3	$FeBr_2$	$HCONH_2$	17.8
4	$FeBr_2$	$EtCONH_2$	25.79

[a]Molar ratio [Fe]: [$RCONH_2$]:[**1**]:[CCl_4]:[MeOH] = 1:50:100:200:50.

favorable effect of methanol on the course of the reaction is due to the in situ formation of MeOCl.

An alternative approach, we have developed, represents a convenient and advantageous procedure, which allows preparation of mono- and difluorobenzyl chlorides (24–65% yield) under mild reaction conditions (20 °C, 3 h) by chlorination of mono- and difluorotoluenes with *tert*-butyl hypochlorite in the presence of

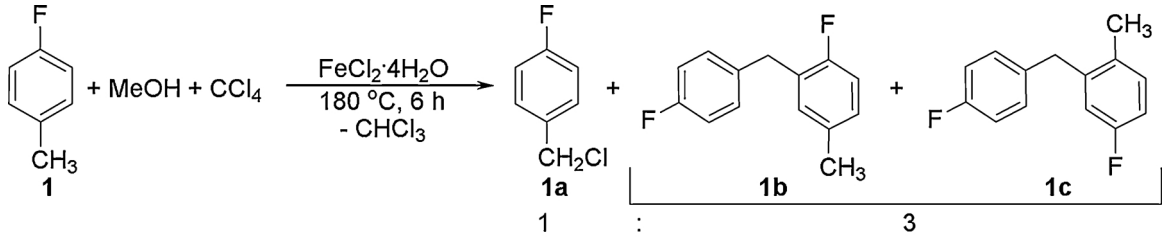
Table 4
Yield of *p*-fluorobenzyl chloride **1a** in the reaction of *p*-fluorotoluene **1** with *t*-BuOCl as a function of temperature and catalyst nature (the reaction time is 3 h).



1 **1a**

Entry	Molar ratio [$FeCl_2{\cdot}4H_2O$]:[**1**]:[*t*-BuOCl]	T, °C	Catalyst	Conversion of **1**, %	Yield of **1a**, %
1	1:100:100	20	$FeCl_2{\cdot}4H_2O$	60	56
2	1:100:300	20	$FeCl_2{\cdot}4H_2O$	70	65
3	0:100:100	20	–	5	5
4	0:100:300	20	–	8	8
5	1:100:100	80	$FeCl_2{\cdot}4H_2O$	72	70
6	1:100:300	80	$FeCl_2{\cdot}4H_2O$	74	70
7	0:100:100	80	–	6	2
8	1:100:100	150*	$FeCl_2{\cdot}4H_2O$	48	44
9	0:100:100	150*	–	44	37
10	1:100:100	20	$FeBr_2$	45	42
11	0:100:100	80	–	5	5
12	1:100:100	80	$FeBr_2$	66	56
13	0:100:100	150*	–	37	37
14	1:100:100	150*	$FeBr_2$	49	44

* the reaction was carried out in an autoclave for 6 h.



$[FeCl_2{\cdot}4H_2O]$: [**1**]: $[CCl_4]$: [MeOH] = 1: 100: 200: 50

Scheme 3. Reaction of *p*-fluorotoluene **1** with MeOH and CCl_4 in the presence of $FeCl_2{\cdot}4H_2O$.

Table 5
Experimental results on the synthesis of mono- and difluorobenzyl chlorides **1a-6a** by chlorination of mono- and difluorotoluenes **1–6** with *t*-BuOCl catalyzed by $FeCl_2{\cdot}4H_2O$ (conditions: 20 °C, 3 h).[a].

Entry	(Di)fluorotoluene **1-6**	Conversion of **1-6**, %	Yield of **1a-6a**, %
1	*p*-Fluorotoluene **1**	70	65
2	*m*-Fluorotoluene **2**	58	31
3	*o*-Fluorotoluene **3**	59	36
4	2,4-Difluorotoluene **4**	55	33
5	2,5-Difluorotoluene **5**	51	24
6	2,6-Difluorotoluene **6**	61	36

[a]Molar ratio [$FeCl_2{\cdot}4H_2O$]:[**1–6**]:[*t*-BuOCl] = 1:100:300.

$FeCl_2{\cdot}4H_2O$ catalyst.

4. Experimental

4.1. General

^1H, ^{13}C and ^{19}F NMR spectra were recorded in $CDCl_3$ using a Bruker-Avance-400 NMR spectrometer (400.1, 100.6 and 376.4 MHz, respectively and a Bruker-Avance-500 NMR spectrometer (500.2, 125.8 and 470.6 MHz, respectively). Chemical shifts (δ) are given in ppm and referenced relative to TMS. Mass spectra were run on were acquired with a Shimadzu GCMS-QP2010Plus GC/MS spectrometer (an SPB-5 capillary column, 30 m × 0.25 mm, helium as a carrier gas, temperature programming from 40 to 300 °C at 8 °C/min, evaporation temperature 280 °C, temperature of the ion source 200 °C, ionization energy 70 eV). Chromatographic analysis was performed on a Shimadzu GC-9A, GC-2014 instrument [2 m × 3 mm column, silicone SE-30 (5%) on Chromaton N-AW-HMDS as the stationary phase, temperature programming from 50 to 270 °C at 8 °C/min, helium as the carrier gas (47 mL/min)].

To identify compounds **1a-6a** and **1b, c** combined samples obtained in experiments 3–6 were used.

4.2. Preparation of mono- and difluorobenzyl chlorides

4.2.1. General procedures

Method A. The reactions were carried out in a glass tube (V = 10 mL) placed into a stainless steel autoclave (V = 17 mL) at a controlled heating.

The tube under argon was charged with $FeCl_2{\cdot}4H_2O$ (0.09 mmol, 0.018 g) and formamide (4.5 mmol, 0.20 g), the mixture was heated for 5 min, and then tetrachloromethane (18 mmol, 2.76 g), methanol (4.5 mmol, 0.14 g), and fluorotoluene **1–3** (9 mmol, 1.00 g) (or difluorotoluene **4–6** (9 mmol, 1.15 g)) were added. The sealed tube was placed into an autoclave, and the autoclave was sealed and heated for 6 h at 180 °C. After completion of the reaction, the autoclave was cooled down to room temperature, the tube was opened, and the reaction mixture was filtered through a paper filter. The solvent was distilled off. The target product was separated from the initial mono- or difluorotoluenes by vacuum distillation.

Method B. The reactions were carried out in a glass reactor (V = 20 mL) with continuous stirring at room temperature.

The tube under argon was charged with $FeCl_2{\cdot}4H_2O$ (0.18 mmol, 0.036 g), synthesized authentic *tert*-butyl hypochlorite [22] (54 mmol, 5.88 g) and fluorotoluene **1–3** (18 mmol, (2.00 g) (or difluorotoluene **4–6** (2.30 g)). The mixture was stirred at r.t. for 3 h. After completion of the reaction, the reaction mixture was filtered through a paper filter. The target product was separated from the initial mono- or difluorotoluene by vacuum distillation.

The structures of the products were proved by NMR and mass spectrometry and by comparison with authentic samples and reference data.

4.2.2. 4-Fluorobenzyl chloride (1a)

Yield: 0.88 g (67%) (*Method A*), 1.69 g (65%) (*Method B*), colorless liquid: bp 76–78 °C/20 mm (Lit. data: bp 62 °C/10 mm [18]). The NMR spectroscopic data agree with those described in ref. [4,8,9]. ^1H NMR (400.1 MHz, $CDCl_3$): δ 4.6 (s, 2H, CH_2), 7.1 (t, 2H, $^3J_{HH} \approx {}^3J_{HF}$ = 8.5 Hz, $H^{3,5}$), 7.4 (m, 2H, $H^{2,6}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 45.5 (s, CH_2), 115.7 (d, $^2J_{CF}$ = 21,7 Hz, $C^{3,5}$), 130.5 (d, $^3J_{CF}$ = 8,3 Hz, $C^{2,6}$), 133.5 (d, $^4J_{CF}$ = 3.3 Hz, C^1), 162.6 (d, $^1J_{CF}$ = 247.4 Hz, C^4). ^{19}F NMR (376.4 MHz, $CDCl_3$): δ -113.2 (s, 1 F, F^4). MS (EI, 70 eV) *m/z* (%): 144 $[M]^+$ (17), 110 (7), 109 (100), 107 (9), 95 (6), 83 (15).

Difluoroarylmethanes (**1b**, **c**). Yield: 0.69 g (70%) (*Method A, without HCONH*$_2$) (The isomer ratio **1b**:**1c** = 2:1), colorless liquid: bp 115–117 °C/2 mm.

4.2.3. 1-Fluoro-2-(4-fluorobenzyl)-4-methylbenzene (1b)

^1H NMR (500.2 MHz, $CDCl_3$): δ 2.4 (s, 3H, CH_3), 4.0 (s, 2H, CH_2), 6.7–7.7 (m, $7H_{A,B}$). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 20.8 (s, CH_3), 34.2 (s, CH_2), 115.1 (d, $^2J_{CF}$ = 22.9 Hz, C_B^6), 115.3 (d, $^2J_{CF}$ = 21.1 Hz, $C_A^{3,5}$), 128.6 (d, $^3J_{CF}$ = 7.6 Hz, C_B^5), 130.2 (d, $^3J_{CF}$ = 7.4 Hz, $C_A^{2,6}$, C_B^3), 131.4 (s, C_B^2), 133.6 (s, C_A^1), 135.8 (s, C_A^1), 159.2 (d, $^1J_{CF}$ = 242.8 Hz, C_B^1), 161.5 (d, $^1J_{CF}$ = 244.0 Hz, C_A^4). ^{19}F NMR (470.6 MHz, $CDCl_3$): δ -117.0 (s, 1 F), -123.2 (s, 1 F), F_B^1 and F_A^4. MS (EI, 70 eV) *m/z* (%): 218 $[M]^+$ (100), 217 (17), 203 (97), 201 (25), 183 (25), 109 (25).

4.2.4. 4-Fluoro-2-(4-fluorobenzyl)-1-methylbenzene (1c)

^1H NMR (500.2 MHz, $CDCl_3$): δ 2.3 (s, 3H, CH_3), 3.9 (s, 2H, CH_2), 6.7–7.7 (m, $7H_{A,B}$). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 19.0 (s, CH_3), 38.7 (s, CH_2), 115.3 (d, $^2J_{CF}$ = 21.1 Hz, $C_A^{3,5}$), 115.4 (d, $^2J_{CF}$ = 21.0 Hz, C_B^5), 127.5 (d, $^2J_{CF}$ = 16.0 Hz, C_B^3), 128.6 (d, $^3J_{CF}$ = 7.6 Hz, C_B^6), 130.2 (d, $^3J_{CF}$ = 7.4 Hz, $C_A^{2,6}$), 131.6 (s, C_B^1), 132.0 (s, C_A^1), 135.2 (s, C_B^2), 161.4 (d, $^1J_{CF}$ = 243.9 Hz, C_B^4), 161.5 (d, $^1J_{CF}$ = 244.0 Hz, C_A^4). ^{19}F NMR (470.6 MHz, $CDCl_3$): δ -116.9 (s, 1 F), -117.5 (s, 1 F), F_A^4 and F_B^4. MS (EI, 70 eV) *m/z* (%): 218 $[M]^+$ (100), 217 (17), 203 (97), 201 (25), 183 (25), 109 (25).

4.2.5. 3-Fluorobenzyl chloride (2a)

Yield: 0.46 g (35%) (*Method A*), 0.81 g (31%) (*Method B*), colorless liquid: bp 68–69 °C/14 mm (Lit. data: bp 60 °C/10 mm [18]). ^1H NMR (400.1 MHz, $CDCl_3$): δ 4.6 (s, 2H, CH_2), 7.0 (dd, 1H, $^3J_{HF}$ = 9.0 Hz, $^3J_{HH}$ = 8.0 Hz, H^4), 7.1 (d, 1H, $^3J_{HF}$ = 9.0 Hz, H^2), 7.2 (d, 1H, $^3J_{HH}$ = 8.0 Hz, H^6), 7.3 (t, 1H, $^4J_{HF}$ = 8.0 Hz, $^3J_{HH}$ = 8.0 Hz, H^5). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 45.3 (s, CH_2), 115.3 (d, $^2J_{CF}$ = 20.9 Hz, C^4), 115.5 (d, $^2J_{CF}$ = 21.9 Hz, C^2), 124.1 (d, $^4J_{CF}$ = 3.0 Hz, C^6), 130.3 (d, $^3J_{CF}$ = 8.2 Hz, C^5), 139.8 (d, $^3J_{CF}$ = 7.4 Hz, C^1), 162.8 (d, $^1J_{CF}$ = 246.7 Hz, C^3). ^{19}F NMR (376.4 MHz, $CDCl_3$): δ -112.5 (s, 1 F, F^3). MS (EI, 70 eV) *m/z* (%): 144 $[M]^+$ (25), 109 (100), 107 (11), 83 (25), 63 (7), 57 (9).

4.2.6. 2-Fluorobenzyl chloride (3a)

Yield: 0.40 g (30%) (*Method A*), 0.94 g (36%) (*Method B*), colorless liquid: bp 72–73 °C/20 mm (Lit. data: bp 59 °C/10 mm [18]). ^1H NMR (500.2 MHz, $CDCl_3$): δ 4.7 (s, 2H, CH_2), 7.1–7.2 (m, 1H, H^3), 7.2 (t, 1H, ^3J = 8.0 Hz, H^5), 7.3–7.4 (m, 1H, H^4), 7.5 (t, 1H, ^3J = 8.0 Hz, H^6). ^{13}C NMR (125.8 MHz, $CDCl_3$): δ 39.5 (d, $^3J_{CF}$ = 4.6 Hz, CH_2), 115.7 (d, $^2J_{CF}$ = 21.1 Hz, C^3), 124.5 (d, $^4J_{CF}$ = 3.8 Hz, C^5), 124.8 (d, $^2J_{CF}$ = 14.3 Hz, C^1), 130.6 (d, $^3J_{CF}$ = 8.2 Hz, C^6), 131.0 (d, $^3J_{CF}$ = 3.0 Hz, C^4), 160.7 (d, $^1J_{CF}$ = 249.3 Hz, C^2). ^{19}F NMR (470.6 MHz, $CDCl_3$: δ -117.7 (s, 1 F, F^2). MS (EI, 70 eV) *m/z* (%): 144 $[M]^+$ (20), 110 (8), 109 (100), 107 (9), 83 (20), 57 (6).

4.2.7. 2,4-Difluorobenzyl chloride (4a)

Yield: 0.64 g (44%) (*Method A*), 0.97 g (33%) (*Method B*), colorless liquid: bp 52–53 °C/8 mm (Lit. data: bp 60 °C/10 mm [18]). ^1H NMR (400.1 MHz, $CDCl_3$): δ 4.6 (s, 2H, CH_2), 6.8 (m, 2H, $H^{5,6}$), 7.4 (m, 1H, H^3). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 38.7 (d, $^3J_{CF}$ = 4.0 Hz, CH_2),

104.2 (t, $^{2}J_{CF}$ = 25.4 Hz, C^{3}), 111.7 (dd, $^{2}J_{CF}$ = 21.5 Hz, $^{4}J_{CF}$ = 3.8 Hz, C^{5}), 120.9 (dd, $^{2}J_{CF}$ = 14.7 Hz; $^{4}J_{CF}$ = 3.8 Hz, C^{1}), 131.8 (dd, $^{3}J_{CF}$ = 4.8 Hz; $^{3}J_{CF}$ = 10.0 Hz, C^{6}), 160.8 (dd, $^{1}J_{CF}$ = 252.1 Hz; $^{3}J_{CF}$ = 12.2 Hz, C^{4}), 163.1 (dd, $^{1}J_{CF}$ = 250.5 Hz; $^{3}J_{CF}$ = 12.0 Hz, C^{2}). ^{19}F NMR (376.4 MHz, $CDCl_3$): δ -108.7 (s, 1 F, F^{4}), -113.1 (s, 1 F, F^{2}). MS (EI, 70 eV) *m/z* (%): 162 $[M]^+$ (10), 128 (8), 127 (100), 125 (7), 107 (9), 101 (13).

4.2.8. 2,5-Difluorobenzyl chloride (5a)

Yield: 0.37 g (25%) (*Method A*), 0.70 g (24%) (*Method B*), colorless liquid: bp 57–58 °C/10 mm (Lit. data: bp 77 °C/23 mm [18]). ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 4.6 (s, 2H, CH_2), 6.9–7.2 (m, 3H, $H^{3,4,6}$). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 38.7 (d, $^{3}J_{CF}$ = 4.3 Hz, C^{7}), 116.7 (dd, $^{2}J_{CF}$ = 24.0 Hz, $^{3}J_{CF}$ = 4.0 Hz, C^{4}), 116.8 (dd, $^{2}J_{CF}$ = 24.2 Hz, $^{4}J_{CF}$ = 3.7 Hz, C^{6}), 117.1 (dd, $^{2}J_{CF}$ = 25.0 Hz, $^{3}J_{CF}$ = 3.7 Hz, C^{3}), 126.2 (dd, $^{3}J_{CF}$ = 8.0 Hz; $^{2}J_{CF}$ = 16.9 Hz, C^{1}), 156.4 (dd, $^{1}J_{CF}$ = 245.9 Hz; $^{4}J_{CF}$ = 3.0 Hz, C^{5}), 158.5 (dd, $^{1}J_{CF}$ = 243.6 Hz, $^{4}J_{CF}$ = 3.0 Hz, C^{2}). ^{19}F NMR (376.4 MHz, $CDCl_3$): δ -118.2 (s, 1 F), -123.8 (s, 1 F), F^{2} and F^{5}. MS (EI, 70 eV) *m/z* (%): 162 $[M]^+$ (15), 128 (7), 127 (100), 125 (7), 107 (10), 101 (14).

4.2.9. 2,6-Difluorobenzyl chloride (6a)

Yield: 0.63 g (43%) (*Method A*), 1.05 g (36%) (*Method B*), colorless liquid: bp 54–55 °C/10 mm (Lit. data: bp 76 °C/22 mm [18]). The NMR spectroscopic data agree with those described in ref. [19,23]. ^{1}H NMR (400.1 MHz, $CDCl_3$): δ 4.7 (br. s, 2H, CH_2), 6.9 (t, $^{3}J_{HH} \approx {}^{3}J_{HF}$ = 8.0 Hz, 2H, $H^{3,5}$), 7.3 (m, 1H, H^{4}). ^{13}C NMR (100.6 MHz, $CDCl_3$): δ 32.4 (t, $^{3}J_{CF}$ = 4.7 Hz, C^{7}), 111.5 (m, $C^{3,5}$), 114.1 (t, $^{2}J_{CF}$ = 19.1 Hz, C^{1}), 130.7 (t, $^{3}J_{CF}$ = 10.3 Hz, C^{4}), 161.2 (dd, $^{1}J_{CF}$ = 252.0 Hz; $^{3}J_{CF}$ = 7.0 Hz, $C^{2,6}$). ^{19}F NMR (376.4 MHz, $CDCl_3$): δ -114.9 (br. s, 2 F, $\Delta W_{1/2}$ = 20.0 Hz, $F^{2,6}$). MS (EI, 70 eV) *m/z* (%): 162 $[M]^+$ (15), 128 (7), 127 (100), 126 (2), 125 (6), 57 (6).

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jfluchem.2019.109346.

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