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Aromatic fluoro-de-triazenation with boron trifluoride diethyl etherate under non-protic acid conditions

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ABSTRACT

Fluoro-de-triazenation of 3,3-diethyl-1-aryltriazenes can be achieved by conventional or under microwave heating in carbon tetrachloride, in the presence of boron trifluoride diethyl etherate without any protic acid to avoid corresponding unwanted byproduct formation.

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1. Introduction

Most of the pharmacologically active fluorinated drugs are aromatic, bearing a fluoro or a trifluoromethyl substituent [1]. The efficient regioselective introduction of fluorine in electron-rich arenes under mild conditions continues to be a challenge [2,3]. Fluoro-de-triazenation (so called Wallach reaction) represents one of the few regioselective nucleophilic routes yielding arylfluorides (Ar-F) [4]. The triazenes have been known for more than a century and have been studied for their versatility in organic synthesis, especially after their biological activities were first reported in the beginning of the 1960s [5,6]. The 3,3-dialkyl-1-aryltriazenes (Ar–N=N–NR′R″) are regarded as protected form of aryldiazonium ions and therefore their acid-triggered thermal decomposition parallels that of the corresponding diazonium ionic reactions [4,7–10]. The use of 3,3-dialkyl-1-aryltriazenes (Ar–N=N–NR′R″) has an essential advantage over the aryldiazonium ions because of their solubility in a number of anhydrous organic and ionic solvents [4,9,11]. Moreover, they can be safely and readily prepared in moderate to high yields [5,12,13]. In parallel, solid-phase methodologies were also applied for the synthesis and reactivity of resin-bound triazenes [10,14,15]. The 3,3-dialkyl-1-aryltriazenes are regarded as protected form of aryldiazonium ions and therefore their acid-triggered thermal decomposition parallels that of the corresponding diazonium ionic reactions. The reactivity of aryltriazenes is well described, especially the competition between ionic (heterolytic) and radical (homolytic) de-triazenation and de-diazoniation pathways during fluoro-de-diazoniation, mechanism strongly dependents upon the reaction conditions [4,7–10]. As protic acid is usually required to decompose aryltriazene, and since the formed phenyl cation intermediate is highly reactive, fluoro-de-triazenation is often accompanied by the formation of a substantial amount of the acid counterion substituted byproduct (Ar-A) [9,11].

We have been investigating the fluoro-de-triazenation reaction as part of a program toward the synthesis of 5-fluoro-3-(4-phenylpiperidin-1-yl)-1,2,3,4-tetrahydro-naphthalen-2-ol (5-FBVM) [16]. Therein we have proposed that 3,3-diethyl-1-aryltriazene could be thermally decomposed and subsequently regioselectively fluorinated using boron trifluoride diethyl etherate (BF_3•Et_2O) as both Lewis acid and fluorinating agent. Thus, the main advantage of the protocol is the avoidance of the competitive formation of the unwanted compound Ar-A. Using 3,3-diethyl-1-naphthyltriazene as a model, the influence of different organic solvents was studied. Furthermore, to demonstrate the versatility of the method, a fluoro-de-triazenation was successfully performed using conventional and microwave heating on several 4-substituted 3,3-diethyl-1-aryltriazenes.

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2. Results and discussion

2.1. Preparation of 3,3-diethyl-1-aryltriazenes

All 3,3-diethyl-1-aryltriazenes **2a-g** were prepared according to known procedure [13], involving diazotization of aromatic amines **1a-g** with sodium nitrite in acidic aqueous medium at 0–5 °C followed by addition of diethylamine to yield the corresponding triazenes **2a-g** (Table 1).

2.2. Fluoro-de-triazenation with polyphosphoric acid and boron trifluoride diethyl etherate

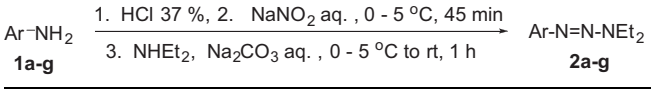
Triflic acid (TfOH) is not an optimal acid for aromatic fluoro-de-triazenation. Besides its incompatibility with the acid-sensitive functional groups, substantial amounts of aryl triflate (Ar-OTf) is usually produced [9,11]. Polyphosphoric acid (PPA) presents a weaker nucleophilic conjugated base (A^-) and with a suitable redox potential to avoid the radical decomposition pathways [4]. Refluxing by using chloroform ($CHCl_3$) instead of dichloromethane (CH_2Cl_2), and by using PPA in the presence of $BF_3{\bullet}Et_2O$ instead of TfOH, the yield of **3a** (5-FBVM) was increased from 25% as previously described [16] to 34% yield (Table 2). We used 3,3-diethyl-1-naphthyltriazene **2b** as a model precursor for 5-FBVM, as in $CHCl_3$, **3b** was obtained in 28% yield compared to only 5% in CH_2Cl_2. PPA looked promising, although it has never been used in fluoro-de-triazenation before. Because of its polymeric nature, we assumed its counter anion (A^-) is a non-nucleophilic species that would prevent the formation of the Ar-A byproduct.

In the presence of PPA, we observed that the triazenes **2a,b** were stable before the addition of $BF_3{\bullet}Et_2O$. With this observation in hand, along with the theoretical study of the coordination chemistry of triazene derivatives [17–19], and electron donor–acceptor (EDA) complexes between BF_3 and methylated ammonia derivatives [20–22], we proposed that the fluorination of the 3,3-dialkyl-1-aryltriazenes was possible using $BF_3{\bullet}Et_2O$ only, as depicted by the proposed reaction mechanism in Scheme 1.

The first rate limiting step is probably the reversible coordination of the BF_3, due to its electrophilicity and affinity toward nitrogen, at N(3) triazene which destabilizes the N(2)–-N(3) bond by inhibiting delocalization across the triazene linkage [23] and, therefore, induces its breakage, expelling BF_2NEt_2 followed in the second step by the formation of the aryldiazonium ion (Scheme 1). As suggested in the literature, the "reorganization energy" present during the pyramidalization (sp^2–sp^3) of the boron atom probably contributes to a reduction in the exothermicity of the complexation reaction [20–22]. Thus, boron trifluoride plays two roles during the reaction: (i) it serves as an electron acceptor toward aryltriazenes to enhance the reactivity of the N(2)–N(3) bond; (ii) it serves as a fluoride source for the regioselective fluorination of the arene.

In spite of a previous work of Saeki et al. [24] where after several tentative experiments, "1-aryltriazenes did not react with boron trifluoride in the absence of either the palladium catalyst or boronic acid", this work gives proofs that fluoro-de-triazenation can be successfully accomplished without any protic acid or catalyst and only in the presence of $BF_3{\bullet}Et_2O$.

Table 1
Synthesis of 3,3-diethyl-1-aryltriazenes **2a-g**. .



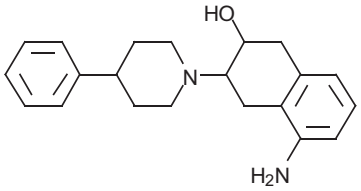
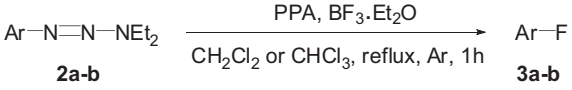
	Ar-NH_2	Triazene (isolated yield %)
1a [16]		**2a** (69)
1b	1-Naphthylamine	**2b** (34)
1c	4-Me-$C_6H_4NH_2$	**2c** (76)
1d	4-NO_2-$C_6H_4NH_2$	**2d** (47)
1e	4-O-C_4H_9-$C_6H_4NH_2$	**2e** (53)
1f	4-I-$C_6H_4NH_2$	**2f** (31)
1g	4-CN-$C_6H_4NH_2$	**2g** (56)

Table 2
Fluoro-de-triazenation using polyphosphoric acid and boron trifluoride diethyl etherate. .

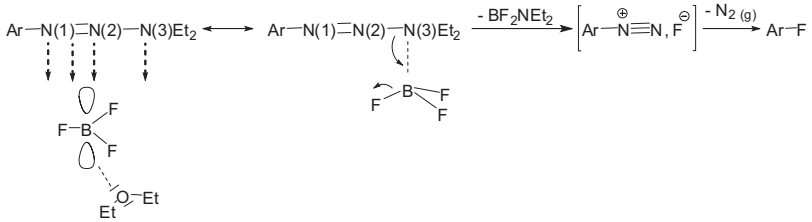


Triazene	Arylfluoride	Yield in CH_2Cl_2 (%)	Yield in $CHCl_3$ (%)
2a	**3a**	34	39
2b	**3b**	5	28

2.3. Fluoro-de-triazenation of 3,3-diethyl-1-aryltriazenes by boron trifluoride diethyl etherate in various solvents

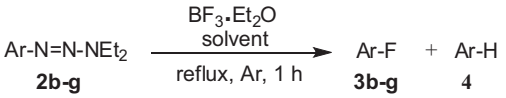
As shown in Table 3 where **2b** was selected as the model precursor, fluorination of **2b-g** was carried out using 1.5 equivalents of $BF_3{\bullet}Et_2O$ at reflux temperature under argon for 1 h in various organic solvents.

By increasing the reaction temperature, reduced cleavage of **2b**, leading to naphthalene **4** as "traceless" byproduct, was suppressed, while the ionic reaction was favored (Table 3). Interesting, in carbon tetrachloride (CCl_4), no radical reaction was observed since **4** was not detected. On the other hand, the radical decomposition pathway was favored over the ionic one in tetrahydrofuran (THF), as THF could act as a reducer as suggested in the literature [4,9,25]. On the contrary, redox potential of CH_3CN is not in favor of any reduction of **2b** or its aryldiazonium ion. But, as proposed and rationalized by Pages et al. [9], **4** could also be the result of redox process(es) between non-complexated triazene and diazonium ion. Furthermore, solvent competition was observed with *t*-butanol (*t*-BuOH), besides 35% of **3b**, formation of 1-*t*-butoxynaphthalene was observed (data not shown).



Scheme 1. Proposed reaction mechanism of fluoro-de-triazenation with 3,3-diethyl-1-aryl triazene and $BF_3{\bullet}Et_2O$.

Table 3
Solvent influence on the yields of **3b-g** in fluoro-de-triazenation of **2b-g**. Ratio of ionic pathway **(3b)** were compared to radical pathway **(4)**. .



Triazene	Aryl-fluoride	Yield in CH_2Cl_2 (%)	Yield in $CHCl_3$ (%)	Yield in CCl_4 (%)	Yield in THF or CH_3CN (%)	Yield in *t*-BuOH (%)
2b	**3b**	8 **3b**/**4**[a]: ~1/2	31 **3b**/**4**[a]: ~1/1	59 **4**: not obs.[b]	Trace **4**: main pdt [c]	35 **4**: not obs.[b]
2c-e	**3c-e**	–	–	0	–	0
2f	**3f**	–	–	30	–	17
2g	**3g**	–	–	0	–	23

[a] Crude molar ratio determined by HPLC analysis, **4** was naphthalene.
[b] Naphthalene was not observed.
[c] Naphthalene was the main product.

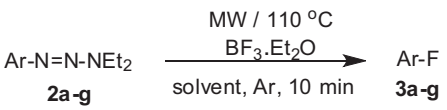
From the solvent effect studies, CCl_4 and *t*-BuOH were chosen as prime solvents to extend the method to (4-substituted phenyl)-triazenes **2c-g** (Table 3). Carrying reactions in CCl_4 and *t*-BuOH did not afford the corresponding Ar-F derivative under chosen reaction conditions for **2c**,**d** and **2e**. Especially for **2d** and **2e,** no triazene decomposition in both examined solvents was detected. In general, the low reactivity of triazenes is reflected in their high temperature of decomposition (>130 °C) [8] and correlates with diazonium salts decomposition (>90 °C) [26], and so is responsible for poor reproducible yields of fluoro-de-diazoniation. On the other hand, **2f** underwent fluoro-de-triazenation successfully in CCl_4 and *t*-BuOH with yields 30% and 17% of 1-fluoro-4-iodobenzene **3f**, respectively. Conducting reactions in *t*-BuOH, 4-fluorobenzonitrile **3g** was produced in 23% yield (Table 3). Unreacted triazene precursor **2g** was found after reflux in CCl_4 in the quenched mixture. Noteworthy, 1-*t*-butoxy-4-iodobenzene and 4-*t*-butoxybenzonitrile were formed in *t*-BuOH (data not shown), coming from solvent competition.

2.4. Microwave assisted fluoro-de-triazenation

Based on the observation that the main problem of the protocol is the high temperature of triazene decomposition, we performed a fluoro-de-triazenation by microwave irradiation to compare results with conventional heating conditions in CCl_4 and *t*-BuOH.

As predicted, microwave irradiation (MW) facilitated the fluorination of **2a-g** using 1.5 equivalent of BF_3•Et_2O in CCl_4 and *t*-BuOH under anhydrous conditions at 110 °C for 10 min (Table 4). For unreacted compounds in conventional heating, the reaction succeeded, and afforded 27% in CCl_4 and 17% in *t*-BuOH of **3d** (Table 4). No reducing products derived from radical pathways were detected in both solvents. As 4-nitrophenyl-cation is electronically more destabilized than the corresponding arene-diazonium ion, we assumed that rapid access to 110 °C and uniform MW dielectric heating allowed immediate formation of aryl cation after triazene complexation which is crucial for a successful fluorination. Efficient MW-assisted fluorination was also observed with **2e** in CCl_4 to give **3e** in 64% yield, but only a 15% yield was observed in *t*-BuOH (Table 4). The reaction in *t*-BuOH of **3c** did not yield the corresponding fluoroarene, but rather 1-*t*-butoxy-4-methylbenzene (data not shown). Yields of the **3b** under MW in both solvents were comparable to the yields obtained under conventional heating. MW fluoro-de-triazenation of **2g** in CCl_4 also afforded 41% yield of **3g** and comparable 16% yield to conventional heating in *t*-BuOH. Under these conditions, reactions afforded significantly higher yields of fluorovesamicol derivative **3a** from previous 25% to 72% in CCl_4 and 54% in *t*-BuOH.

Table 4
Microwave assisted fluoro-de-triazenation of **2a-g**. .



Triazene	Arylfluoride	Isolated yield in CCl_4 (%)	Isolated yield in *t*-BuOH (%)
2a	**3a**	72	54
2b	**3b**	52	21
2c	**3c**	9	0
2d	**3d**	27	17
2e	**3e**	64	15
2f	**3f**	42	32
2g	**3g**	41	16

3. Conclusion

We have performed studies toward rapid and synthetically useful fluorination to obtain 1-fluoronaphthalene, 4-substituted-1-fluorobenzenes and validated the method by obtention of 5-fluoro-3-(4-phenylpiperidin-1-yl)-1,2,3,4-tetrahydro-naphthalen-2-ol from the corresponding 3,3-diethyl-1-aryltriazene precursors in CCl_4 with only boron trifluoride diethyl etherate complex. This advantage distinguishes the present method from numerous precedents where protic acid was necessary. The use of the controlled MW heating could be implemented successfully leading to significant improvement in the reaction efficiency and reaction time in cases where conventional heating in CCl_4 and *t*-BuOH has failed.

4. Experimental

4.1. General information

Column chromatography was used for routine purification of reaction products using silica gel (Merck 60; 0.015–0.040 mm). Preparative TLC was carried out using 20 cm × 20 cm glass backed silica gel F_{254} plates, 1 mm thickness. High-pressure liquid chromatography (HPLC) was carried out on a Beckman system Gold with XBridge™ column (5 μm, 4.6 mm × 150 mm), at a flow rate of 1 mL/min, and a 254 nm ultraviolet detector (0.1 M $NH_4^+CH_3COO^-$/CH_3CN, 55/45). ^1H and ^{13}C NMR spectra were recorded in a $CDCl_3$ solution on a Bruker DPX Avance spectrometer (300 MHz for ^1H, 75 MHz for ^{13}C, and 282 MHz for ^{19}F) at 298 K. ^1H and ^{13}C chemical shifts (δ) are expressed as part per million (ppm) relative to TMS as an internal standard and ^1H spin-spin coupling constants (J) are given in Hertz (Hz). HRMS data were recorded on a

Thermo Scientific Q-Exactive; analyses were done by infusion at 1400 resolution. Microwave syntheses were carried out on a Discover® monomode reactor from CEM Corporation. All reagents, chemicals and solvents were used as received from commercial suppliers.

Compounds **2a** [16], **2c** [13], **2d** [27], and **2g** [13] were characterized as previously described. The spectral data of fluoroaryl derivatives **3b-d, f, g** were identical to those obtained from the commercial product, and could be observed by web software SciFinder® (Copyright© 2012 American Chemical Society) in «Experimental Properties» from the CAS REGISTRY.

4.2. General procedure for preparation of 3,3-diethyl-1-aryltriazenes **2a-g**

In a round bottom flask, arylamine **1a-g** (35 mmol), aqueous hydrochloric acid (37%, 8.7 mL, 105 mmol) and water (90 mL) were added. The resulting mixture was cooled to 0–5 °C and a chilled water solution of $NaNO_2$ (25 mL, 2.96 g of $NaNO_2$, 42 mmol) was added dropwise while maintaining the temperature below 5 °C. The mixture was left to stir for 45 min at 0–5 °C, after which it was neutralized by the dropwise addition of a cold saturated solution of Na_2CO_3 (10 mL) and diethylamine (5.4 mL, 52.5 mmol) in chilled water (30 mL). After stirring for 1 h, the reaction mixture was extracted with CH_2Cl_2 (3× 90 mL). Combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure to give a crude residue which was chromatographically purified to furnish **2a-g**. Triazenes **2a-g** were stored at −20 °C, in the dark to avoid decomposition.

4.2.1. 3,3-Diethyl-1-naphthyltriazene **2b**

Compound **2b** was purified by column chromatography (EtOAc/*n*-heptane, 1/3) to give **2b** (34%) as a red oil; ^{1}H NMR ($CDCl_3$): δ 1.38 (t, J = 7.1 Hz, 6H), 3.90 (q, J = 7.1 Hz, 4H), 7.45–7.51 (m, $4H_{Ar}$), 7.66 (dd, J = 6.6 Hz, J = 2.6 Hz, $1H_{Ar}$), 7.82–7.86 (m, $1H_{Ar}$), 8.60–8.63 (m, $1H_{Ar}$); ^{13}C NMR ($CDCl_3$): δ 11.1 (brs, $2CH_3$), 42.0 (brs, $2CH_2$), 111.4, 123.7, 124.8, 125.1, 125.7, 126.0, 127.6, 129.4, 134.3, 146.5; HRMS: calculated $[M+H]^+$ for $C_{14}H_{17}N_3$: 228.14952, found: 228.15182.

4.2.2. 3,3-Diethyl-1-(4-butoxyphenyl)triazene **2e**

Compound **2e** was purified by column chromatography (EtOAc/*n*-heptane, 1/5) to give **2e** (53% yield) as a red oil; ^{1}H NMR ($CDCl_3$): δ 1.00 (t, J = 7.2 Hz, 3H), 1.27 (t, J = 7.2 Hz, 6H), 1.47–1.57 (m, 2H), 1.75–1.82 (m, 2H), 3.75 (q, J = 7.2 Hz, 4H), 3.98 (t, J = 7.2 Hz, 2H), 6.89 (d, J = 6.9 Hz, $2H_{Ar}$), 7.38 (d, J = 6.9 Hz, $2H_{Ar}$); ^{13}C NMR ($CDCl_3$): δ 11.2 (brs, $2CH_3$), 13.8, 19.2, 31.3, 42.2 (brs, $2CH_2$), 67.9, 114.6 ($2CH_{Ar}$), 121.2 ($2CH_{Ar}$), 144.9, 156.9; HRMS: calculated $[M+H]^+$ for $C_{14}H_{23}N_3O$: 250.19139, found: 250.19389.

4.2.3. 3,3-Diethyl-1-(4-iodophenyl)triazene **2f**

Compound **2f** was purified by column chromatography (EtOAc/*n*-heptane, 1/6) to give **2f** (31% yield) as a red-orange oil; ^{1}H NMR ($CDCl_3$): δ 1.28 (t, J = 7.2 Hz, 6H), 3.77 (q, J = 7.2 Hz, 4H), 7.19 (d, J = 8.7 Hz, $2H_{Ar}$), 7.64 (d, J = 8.7 Hz, $2H_{Ar}$); ^{13}C NMR ($CDCl_3$): δ 11.4 (brs, $2CH_3$), 48.4 (brs, $2CH_2$), 88.9, 122.4 ($2CH_{Ar}$), 137.6 ($2CH_{Ar}$), 150.8; HRMS: calculated $[M+H]^+$ for $C_{10}H_{14}IN_3$: 304.03052, found: 304.03350.

4.3. Typical procedure for the reaction of 3,3-diethyl-1-aryltriazene **2a, 2b** with polyphosphoric acid and boron trifluoride diethyl etherate

In CH_2Cl_2 or $CHCl_3$ (5 mL), 5-fluoro-3-(4-phenylpiperidin-1-yl)-1,2,3,4-tetrahydro-naphthalen-2-ol **2a** (100 mg, 0.25 mmol) was dissolved. This solution was added to polyphosphoric acid 115% (70 mg), under argon atmosphere in a dry two-necked round bottom flask. The mixture was left stirring for 5 min at room temperature followed by BF_3•Et_2O (0.047 mL, 0.375 mmol) addition. After refluxing for 1 h, the reaction mixture was quenched with a saturated Na_2CO_3 aqueous solution (5 mL), extracted with CH_2Cl_2 (3× 5 mL) and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the residue was purified by column chromatography (EtOAc/*n*-heptane, 1/5) to give **3a**.

Compound **3b** was obtained from the same procedure from **2b** (114 mg, 0.5 mmol), in CH_2Cl_2 or $CHCl_3$, leading to **3b** (4 or 20 mg) in 5% or 28% yield, respectively. The spectral data of **3b** were identical to those obtained from the commercial product.

4.3.1. 5-Fluoro-3-(4-phenyl-piperidin-1-yl)-1,2,3,4-tetrahydronaphthalen-2-ol: **3a**

White powder (34% yield in CH_2Cl_2, 39% yield in $CHCl_3$). Identical spectral data to those described in literature [16]. ^{19}F NMR ($CDCl_3$) δ −117.30 ppm (1F).

4.4. General procedure for the reaction of 3,3-diethyl-1-aryltriazene **2b-g** with boron trifluoride diethyl etherate

Under argon atmosphere, 3,3-diethyl-1-aryltriazene **2b-g** (0.50 mmol) was dissolved in 5 mL of solvent (CH_2Cl_2, $CHCl_3$, CCl_4, THF, CH_3CN, or *t*-BuOH) in a dry two-necked round bottomed. While stirring, BF_3•Et_2O (0.10 mL, 0.75 mmol) was added and the reaction was left to stir for 5 min, at room temperature. The reaction mixture was then refluxed under argon for 1 h. After cooling, saturated Na_2CO_3 aqueous solution (5 mL) was added to the crude mixture and extracted with CH_2Cl_2 (3× 5 mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The yields of **3b** were determined by HPLC from standards (8% yield in CH_2Cl_2, 31% yield in $CHCl_3$, 59% yield in CCl_4, negligible yields in THF and CH_3CN, and 35% yield in *t*-BuOH). Yields of **3f** and **3g** were determined by ^{1}H NMR from the crude products (**3f**: 30% yield in CCl_4 and 17% yield in *t*-BuOH; **3g**: 23% yield in *t*-BuOH). The spectral data of **3b**, **3g, 3f** and **4** were identical to commercial products.

4.5. General procedure for the microwave-assisted fluorination of 3,3-diethyl-1-(4-substituted aryl)triazenes **2**

Vial (10 mL) containing magnetic stirring bar was charged with **2b-e** (1.3 mmol), 4 mL of the solvent (CCl_4 or *t*-BuOH) and BF_3•Et_2O (0.25 mL, 1.95 mmol) under an argon atmosphere. The microwave tube was immediately sealed with a silicon septum and placed in the microwave (MW) cavity (Discover®, CEM) and subjected to MW irradiation for 10 min at 110 °C (ramp time 2 min, 20 W). After cooling to room temperature, the reaction mixture was quenched with saturated Na_2CO_3 aqueous solution (5 mL) and extracted with CH_2Cl_2 (3× 5 mL). After drying over $MgSO_4$ and removal of the solvent under reduced pressure, the crude residues **3c-e** were purified by column chromatography (*n*-heptane 100% to EtOAc/*n*-heptane, 1/5) to obtain pure products (yields in CCl_4: **3b**: 52%; **3c**: 9%; **3d**: 27%; **3e**: 64%; **3f**: 42%; **3g**: 41% and yields in *t*-BuOH: **3b**: 21%; **3d**: 17%; **3e**: 15%; **3e**: 32%; **3g**: 16%). The spectral data of **3c** and **3d** were identical to commercial products.

Compound **3a** was obtained from the same procedure from **2a** (30 mg, 0.074 mmol), in CCl_4 and *t*-BuOH, leading, after purification on preparative TLC (EtOAc/*n*-heptane, 1/4), to **3a** (17 and 13 mg) in 72% and 54% yield, respectively.

4.5.1. 1-Butoxy-4-fluorobenzene **3e**

Pale yellow oil (64% yield in CCl_4, 15% yield in *t*-BuOH); ^{1}H NMR ($CDCl_3$) δ 0.96 (t, J = 7.4 Hz, 3H), 1.43–1.52 (m, 2H), 1.71–1.78 (m, 2H), 3.90 (t, J = 6.5 Hz, 2H), 6.79–6.97 (m, $4H_{Ar}$); ^{13}C NMR ($CDCl_3$): δ 13.9, 19.2, 31.3, 68.3, 115.4 (d, J = 8 Hz, $2CH_{Ar}$), 115.7 (d, J = 23 Hz, $2CH_{Ar}$), 155.9, 156.5 (d, J = 250 Hz); ^{19}F NMR ($CDCl_3$) δ −152.08;

HRMS: calculated $[M+H]^+$ for $C_{10}H_{13}FO$: 169.10232, found: 169.10398.

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