

**SELECTFLUOR™ F-TEDA-BF<sub>4</sub> MEDIATED INTRODUCTION OF  
PERFLUOROALKYL-CONTAINING GROUPS IN THE BENZYLIC POSITION  
OF HEXAMETHYLBENZENE**

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Received 18-02-2002

**Abstract**

An effective synthetic pathway for direct introduction of a perfluoroalkyl moiety-containing functional groups at the benzylic position in hexamethylbenzene involved treatment of 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (*Selectfluor™ F-TEDA-BF<sub>4</sub>*) with hexamethylbenzene in the presence of polyfluoro alcohols or potassium salts of perfluoroalkane carboxylic acids.

**Introduction**

Bonding of fluorine atoms to organic molecules dramatically changes their physical properties and chemical and biological reactivities, thus giving a constant impetus to basic and applied research in the field of the organic chemistry of fluorine compounds,<sup>1,2</sup> as manifested in comprehensive commercial applications of fluorinated organic materials.<sup>3,4</sup> The properties of compounds containing the perfluoroalkyl (R<sub>f</sub>) group are considerably different from those of their hydrocarbon or partially fluorinated counterparts. These differences are the result of the high ionization potential of the fluorine atom, its extreme electronegativity and low polarizability, implying the stability, very weak intermolecular forces and low surface energy of perfluoroalkylated organic compounds. Due to the importance of these kinds of materials many reagents and methods for introducing the R<sub>f</sub> group into organic molecules have been developed and the results reviewed.<sup>1,3,4,5</sup>

The introduction of organic molecules bearing a reactive N-F bond as selective fluorinating reagents under mild reaction conditions was very soon followed by their versatile application in synthetic organic chemistry.<sup>1,6</sup> N-F organic compounds possess moderate to strong oxidative power<sup>7</sup> which might cause a certain competition between fluorination and oxidation of the target molecule, but, on the other hand, opens the

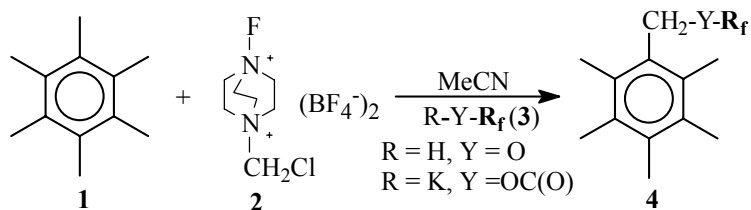
possibility for the use of N-F reagents as mediators of several other types of functionalisation of organic compounds.<sup>8,9</sup> We now report that one of the most popular N-F reagents, 1-chloromethyl-4-fluoro-1,4-diazoniabicyclo[2.2.2]octane bis(tetrafluoroborate) (**1**), known under the commercial name of *Selectfluor*<sup>TM</sup> F-TEDA-BF<sub>4</sub><sup>10</sup>, could be used as a mediator for introduction of some perfluoro functional groups at the benzylic position in hexamethylbenzene.

### Results and Discussion

We recently developed a synthetic method for effective and versatile direct functionalisation of the benzylic position in hexamethylbenzene (HMB) mediated by N-F reagents in the presence of alcohols, carboxylic acids or nitriles as the source of nucleophiles.<sup>9</sup> Although the formation of the corresponding pentamethylbenzyl ether (**4a**, **Table**) after reaction in the presence of 2,2,2-trifluoroethanol was not so effective as when using ethanol, the only moderate drop of efficiency of the reaction encouraged us to extend this method to the introduction of perfluoroalkyl-containing functional groups. In a typical experiment we treated HMB with F-TEDA-BF<sub>4</sub> in a mixture of acetonitrile and a polyfluoro alcohol (MeCN/R<sub>f</sub>OH 9.5 : 0.5) and established that the use of 2,2,3,3,3-pentafluoropropan-1-ol, 1*H*,1*H*-heptafluoro-1-butanol, as well as hexafluoroisopropanol, gave the expected pentamethylbenzyl ethers **4b**, **4c** and **4d** in high yield. Unfortunately, reactions in the presence of higher polyfluorinated *n*-alcohols (hexanol, decanol ...) or perfluoro-*tert*-butanol resulted in the formation of reaction mixtures too complex to have any synthetic value.

The reaction of HMB with F-TEDA-BF<sub>4</sub> in trifluoroacetic acid readily gave pentamethylbenzyl trifluoroacetate (**4e**) almost quantitatively. For the preparation of the corresponding pentamethylbenzyl perfluoroalkyl esters (**4f-i**) we had to use potassium salts of perfluorocarboxylic acids (R = K, **Table**) and MeCN as solvent, since reactions in the pure acids would be too inconvenient, whereas in a MeCN/acid mixture Ritter-type benzylic amidation was observed to take place<sup>9</sup>. Under these reaction conditions esters **4f-4i** were formed in high to excellent yield.

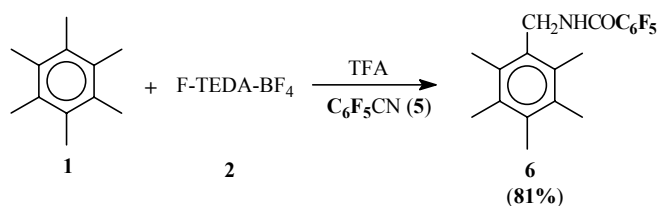
**Table:** Reaction of hexamethylbenzene with F-TEDA-BF<sub>4</sub> (**2**) in MeCN<sup>a)</sup> in the presence of polyfluoroalkylalcohols or potassium salts of perfluoroalkyl carboxylic acid at 55 °C



Entry	<b>3</b>	R	Y	R <sub>f</sub>	Reaction time (min)	Yield <sup>b)</sup> of <b>4</b> (%)
1	<b>a</b>	H	O	CF <sub>3</sub> CH <sub>2</sub>	75	75
2	<b>b</b>	H	O	CF <sub>3</sub> CF <sub>2</sub> CH <sub>2</sub>	80	70
3	<b>c</b>	H	O	CF <sub>3</sub> (CF <sub>2</sub> ) <sub>2</sub> CH <sub>2</sub>	80	70
4	<b>d</b>	H	O	(CF <sub>3</sub> ) <sub>2</sub> CH	120	71
5	<b>e</b>	H	OC(O)	CF <sub>3</sub>	30	97
6	<b>f</b>	K	OC(O)	CF <sub>3</sub> CF <sub>2</sub>	60	97
7	<b>g</b>	K	OC(O)	CF <sub>3</sub> CF <sub>2</sub> CF <sub>2</sub>	90	72
8	<b>h</b>	K	OC(O)	CF <sub>3</sub> (CF <sub>2</sub> ) <sub>4</sub>	75	96
9	<b>i</b>	K	OC(O)	CF <sub>3</sub> (CF <sub>2</sub> ) <sub>6</sub>	60	90

<sup>a)</sup> in the case of **3e** (entry 5) the solvent was TFA; <sup>b)</sup> from the <sup>19</sup>F nmr spectra of crude reaction mixtures using octafluoronaphthalene as internal reference

Further, we tried to apply the protocol for benzylic amidation of HMB<sup>9</sup> using perfluorinated nitriles. Unfortunately the reactions with perfluoroalkanenitriles failed; with pentafluorobenzonitrile (**5**), however, 2,3,4,5,6-pentafluoro-N-(pentamethylbenzyl)benzamide (**6**, **Scheme**) was obtained in high yield.



Scheme

## Experimental

Selectfluor<sup>TM</sup> F-TEDA-BF<sub>4</sub>, polyfluorinated alcohols **3a-d**, perfluorinated acids **3e-i**, and pentafluorobenzonitrile **5** were purchased from Apollo and used as received. Preparative GLC was carried out on a Varian 3300 instrument. <sup>1</sup>H and <sup>19</sup>F NMR spectra were recorded on a Varian 360L spectrometer using TMS and CCl<sub>3</sub>F as internal standards, respectively, at 60 MHz for <sup>1</sup>H and 56.4 MHz for <sup>19</sup>F resonance. IR spectra were recorded on a Perkin Elmer 1310 spectrometer using KBr as supporting material. Mass spectral measurements were carried out on an Autospec Q instrument using electron ionisation (EI) at 70 eV. Melting points were determined on a Büchi 535 apparatus and are uncorrected. Elemental analyses were carried out on a Perkin-Elmer 2400 CHN analyser.

### Synthesis of Pentamethylbenzyl Polyfluoroalkyl Ethers: General Procedure

HMB **1** (2 mmol) and F-TEDA-BF<sub>4</sub> **2** (2 mmol) were dissolved in 19 mL of MeCN, 1 mL of polyfluorinated alcohol **3a**, **3b**, **3c** or **3d** was added and the solution stirred at 55 °C until KI-starch paper showed consumption of **2** (0.5-2 hours). The solvent was removed under reduced pressure, the crude reaction mixture dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL), insoluble material filtered off, the solution washed with water (25 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvent evaporated in vacuo. The pure products **4a-d** were isolated from the thus obtained crude reaction mixtures by preparative gas chromatography (FFAP 5%, Chromosorb W/AW 80/100, T = 130 °C) in order to obtain satisfactory elemental analyses.

#### *Pentamethylbenzyl 2,2,2-trifluoroethyl ether (4a)*

White crystals, mp 70-72 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ(ppm): 2.2 (s, 3H), 2.3 (s, 12H), 3.8 (q, J=9.4 Hz, 2H), 4.8 (s, 2H). <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ(ppm): -75.0 (t, J=9.4 Hz, 3F). MS: m/z: 260 (M<sup>+</sup>, 35%), 245 (20), 161 (100), 160 (95), 145 (25), 91 (18). IR(cm<sup>-1</sup>): 1280, 1155, 1110, 990. Anal. Calcd for C<sub>14</sub>H<sub>19</sub>F<sub>3</sub>O: C, 64.59%; H, 7.36%. Found: C, 64.28%; H, 7.41%.

*2,2,3,3-Pentafluoropropyl pentamethylbenzyl ether (4b)*

White crystals, mp 60-62 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ(ppm): 2.2 (s, 3H), 2.3 (s, 12H), 4.0 (t, J=9.4 Hz, 2H), 4.8 (s, 2H). <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ(ppm): -84.2 (broad s, 3F), -123.7 (t, J=9.4 Hz, 2F). MS: m/z: 310 (M<sup>+</sup>, 50%), 295 (25), 161 (93), 160 (100), 145 (26), 91 (23). IR(cm<sup>-1</sup>): 1250, 1185, 1150, 1100, 1040, 975. HRMS: m/z calcd for C<sub>15</sub>H<sub>19</sub>F<sub>5</sub>O (M<sup>+</sup>): 310.1356; found: 310.1366.

*2,2,3,3,4,4,4-Heptafluorobutyl pentamethylbenzyl ether (4c)*

White crystals, mp 67-68 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ(ppm): 2.3 (s, 3H), 2.4 (s, 12H), 4.0 (t, J=9.4 Hz, 2H), 4.8 (s, 2H). <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ(ppm): -81.3 (t, J=9.4 Hz, 3F), -120.7 (m, 2F), -128.0 (broad s, 2F). MS m/z(relative intensity): 360 (M<sup>+</sup>, 45%), 345 (25), 161 (92), 160 (100), 145 (25), 91 (17). IR(cm<sup>-1</sup>): 1230, 1170, 1110, 995. Anal. Calcd for C<sub>16</sub>H<sub>19</sub>F<sub>7</sub>O: C, 53.33%; H, 5.32%. Found: C, 53.32%; H, 5.15%.

*Pentamethylbenzyl 2,2,2-trifluoro-1-(trifluoromethyl)ethyl ether (4d)*

White crystals, mp 87-88 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ(ppm): 2.3 (s, 3H), 2.4 (s, 12H), 4.1 (sept, J=6.6 Hz, 1H), 5.0 (s, 2H). <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ(ppm): -74.7 (d, J=6.6 Hz, 6F). MS m/z(relative intensity): 328 (M<sup>+</sup>, 60%), 313 (20), 161 (100), 160 (50), 145 (12), 91 (16), 69 (26). IR (cm<sup>-1</sup>): 1280, 1220, 1180, 1110, 1090, 970. Anal. Calcd for C<sub>15</sub>H<sub>18</sub>OF<sub>6</sub>: C, 54.88%; H, 5.53%. Found: C, 54.61%; H, 5.44%.

**Synthesis of Pentamethylbenzyl Perfluoroalkyl Esters: General Procedure**

Aqueous solutions of perfluorocarboxylic acids **3f-i** (R=H) were neutralised by KOH (10% in water), water evaporated by slow heating and potassium salts **3f-i** thus obtained dried in vacuo for a few hours. HMB **1** (2 mmol), F-TEDA-BF<sub>4</sub> **2** (2.2 mmol) and **3f**, **3g**, **3h** or **3i** (2.4 mmol) were dissolved in 20 mL of MeCN (in the case of preparation of **4e** TFA (**3e**) was used as solvent) and the solution stirred at 55 °C until KI-starch paper showed consumption of **2** (0.5-2 hours). The solvent was removed under reduced pressure, the crude reaction mixture dissolved in CH<sub>2</sub>Cl<sub>2</sub> (50 mL), insoluble material filtered off, the solution washed twice with 5% aqueous KOH (25 ml) and water (25 mL), dried over anhydrous Na<sub>2</sub>SO<sub>4</sub>, and the solvent evaporated in vacuo. The pure

products **4d-h** were isolated from the crude reaction mixtures thus obtained by gas chromatography (FFAP 5%, Chromosorb W/AW 80/100, T=130 °C). Data for pentamethylbenzyl trifluoroacetate **4e** were in agreement with those already published<sup>11</sup>, while products **4f-i** were crystallised from methanol in order to obtain satisfactory elemental analyses.

*Pentamethylbenzyl pentafluoropropanoate (4f)*

White crystals, mp 125-126.5 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ(ppm): 2.2 (s, 6H), 2.3 (s, 9H), 5.5 (s, 2H). <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ(ppm): -83.8 (t, J=1.5 Hz, 3F), -121.7 (q, J=1.5 Hz, 2F). MS m/z(relative intensity): 324 (M<sup>+</sup>, 60%), 161 (100), 160 (90), 145 (18), 91 (15), 69 (20). IR (cm<sup>-1</sup>): 1765, 1300, 1220, 1180, 1145, 1020, 900. Anal. Calcd for C<sub>15</sub>H<sub>17</sub>F<sub>5</sub>O<sub>2</sub>: C, 55.55%; H, 5.28%. Found: C, 55.79%; H, 5.12%.

*Pentamethylbenzyl heptafluorobutanoate (4g)*

White crystals, mp 73-74 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ(ppm): 2.2 (s, 6H), 2.3 (s, 9H), 5.5 (s, 2H). <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ(ppm): -82.0 (t, J = 9.4 Hz, 3F), -120.0 (q, J = 9.4 Hz, 2F), -128.0 (broad s, 2F). MS m/z(relative intensity): 374 (M<sup>+</sup>, 28%), 161 (98), 160 (100), 145 (18), 91 (17), 69 (16). IR(cm<sup>-1</sup>): 1775, 1305, 1265, 1225, 1145, 1120, 900. Anal. Calcd for C<sub>16</sub>H<sub>17</sub>F<sub>7</sub>O<sub>2</sub>: C, 51.34%; H, 4.58%. Found: C, 51.29%; H, 4.47%.

*Pentamethylbenzyl undecafluorohexanoate (4h)*

White crystals, mp 62.5-63.5 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ(ppm): 2.2 (s, 6H), 2.3 (m, 9H), 5.6 (s, 2H). <sup>19</sup>F NMR (CDCl<sub>3</sub>): δ = -81.7 (m, 3F), -118.7 (m, 2F), -123.3 (m, 4F), -126.7 (m, 2F). MS m/z (relative intensity): 474 (M<sup>+</sup>, 27%), 161 (77), 160 (100), 145 (18), 91 (15), 69 (75). IR(cm<sup>-1</sup>): 1772, 1318, 1260, 1220, 1200, 1140, 1100, 900. Anal. Calcd for C<sub>18</sub>H<sub>17</sub>F<sub>11</sub>O<sub>2</sub>: C, 45.58%; H, 3.61%; found: C, 45.87%; H, 3.70%.

*Pentamethylbenzyl pentadecafluorooctanoate (4i)*

White crystals, mp 69.5-71 °C. <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ(ppm): 2.2(s, 6H), 2.3 (s, 9H), 5.7 (s, 2H). <sup>19</sup>F NMR (CDCl<sub>3</sub>) δ(ppm): -81.3 (m, 3F), -119.0 (m, 2F), -121 to -124 (m, 8F), -127.0 (m, 2F). MS m/z (relative intensity): 574 (M<sup>+</sup>, 30%), 161 (98), 160 (100), 145(27),

91 (23), 69 (30). IR( $\text{cm}^{-1}$ ): 1770, 1326, 1200, 1140, 1010, 905. Anal. Calcd for  $\text{C}_{20}\text{H}_{17}\text{F}_{15}\text{O}_2$ : C, 41.82%; H, 2.98%; found: C, 42.39%; H, 2.79%.

#### 2,3,4,5,6-Pentafluoro-N-(pentamethylbenzyl)benzamide (6)

To a solution of 2 mmol of HMB in TFA (20 mL) 6 mmol of pentafluorobenzonitrile (5) and 2 mmol of F-TEDA- $\text{BF}_4$  were added and the reaction mixture was stirred at 55 °C for 2.5 hours. The solvent was removed under reduced pressure and the crude reaction mixture dissolved in 50 mL of  $\text{CH}_2\text{Cl}_2$ , insoluble material filtered off, the solution washed with 2% aqueous KOH (25 mL) and water (25 mL), dried over anhydrous  $\text{Na}_2\text{SO}_4$ , and the solvent evaporated to half its volume. The product 6 was precipitated from this solution by n-hexane, filtered off, dried and crystallised from acetone/n-hexane 1:2.

White crystals, mp 233-235 °C.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$ (ppm): 2.2 (s, 6H), 2.3 (s, 9H), 4.7 (d,  $J=5$  Hz, 2H), 5.9 (broad s, 1H).  $^{19}\text{F}$  NMR ( $\text{CDCl}_3$ ):  $\delta = -140.7$  (m, 2F),  $-151.3$  (tt,  $J=18$  Hz, 2 Hz, 1F),  $-161.0$  (m, 2F). MS  $m/z$  (relative intensity): 371 ( $\text{M}^+$ , 25%), 356 (15), 195 (35), 161 (28), 160 (100), 145 (28), 91 (12). IR ( $\text{cm}^{-1}$ ): 3280, 1650, 1540, 1500, 1320, 1110, 990. Anal. Calcd for  $\text{C}_{19}\text{H}_{18}\text{NF}_5\text{O}$ : C, 61.45%; H 4.89%; N 3.77%; found: C, 60.93%; H, 4.85%; N 3.58%.

### Acknowledgement

The authors are grateful to the Ministry of Education, Science and Sport of the Republic of Slovenia for financial support, and to T. Stipanovič and Prof. B. Stanovnik for elemental combustion analysis.

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#### Povzetek

Reakcije heksametilbenzena z 1-klorometil-4-fluoro-1,4-diazoniabiciklo[2.2.2] oktan bis(tetrafluoro boratom) (*Selectfluor*<sup>TM</sup> *F-TEDA-BF<sub>4</sub>*) ob prisotnosti polifluoro alkoholov ali kalijevih soli perfluoroalkil karboksilnih kislin predstavljajo učinkovito sintetsko metodo za uvedbo funkcionalnih skupin, ki vsebujejo perfluoroalkilno verigo, na benzilno mesto v heksametilbenzenu.