

## A Facile Synthesis of Partly-Fluorinated Alkyl Aryl Ethers: Reaction of Octafluorotoluene or Hexafluorobenzene with $\alpha,\alpha,\omega$ -Trihydroperfluorinated Alcohols

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Fluoroorganic compounds have attracted a great deal of interest due to their peculiar physical and biological properties. Accordingly, development of a synthetic method for the preparation of fluoroorganic compounds with typical characteristics has become an important issue in fluoroorganic chemistry.<sup>1</sup> Perfluorinated trialkylamines and dialkyl ethers have been particularly focused on since they are characterized not only by low freezing points, high volatility, improved electrophysical and thermophysical characteristics but also by an excellent lubricating property.<sup>2</sup> Moreover, some perfluorinated organic compounds are also useful as oxygen-carrying liquids in biology and medicine.<sup>3</sup>

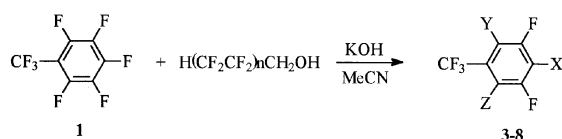
These fluoroorganic compounds have been prepared from hydrocarbon precursors either by electrochemical fluorination<sup>4</sup> or by direct fluorination<sup>5</sup> with F<sub>2</sub>. Unfortunately, those synthetic methodologies provide only low yields of the desired products due to the occurrence of destructive products. On the other hand, fluorination with other chemicals usually requires hazardous and/or expensive fluorinating reagents. It is noteworthy, however, that perfluorination of partly-fluorinated starting materials gives better yields of the desired products because of the lower degree of the destruction process and the easiness of control of fluorination.<sup>6,7</sup> Moreover, several by-products obtained from the polymerization of tetrafluoroethylene or hexafluoroepoxypropylene can be used as starting materials in the synthesis of more complex partly-fluorinated organic compounds.<sup>8</sup> For example,  $\alpha,\alpha,\omega$ -trihydroperfluorinated alcohols, H(CF<sub>2</sub>CF<sub>2</sub>)<sub>n</sub>CH<sub>2</sub>OH, n=1-4, which are the by-products in the synthesis of polytetrafluoroethylene might be good and inexpensive starting materials for the synthesis of partly-fluorinated organic compounds.<sup>9,10,11</sup> The fluorinated alcohols were applied to the reaction with 2,3,4,5,6-pentafluorostyrene/NaH<sup>12</sup>, decafluoroazobenzene/CsF<sup>13</sup> or decafluoro-*m*-dimethylbenzene/NaOH<sup>14</sup>.

In this paper we would like to publish a simple and convenient method for the synthesis of partly-fluorinated alkyl aryl

ethers by using a polyfluorobenzene derivative (octafluorotoluene (**1**) or hexafluorobenzene (**2**)) and  $\alpha,\alpha,\omega$ -trihydroperfluorinated alcohols. The reaction of octafluorotoluene with  $\alpha,\alpha,\omega$ -trihydroperfluorinated alcohols in acetonitrile (or DMF) in the presence of an equimolar amount of KOH provides the fluorinated alkyl aryl ethers **3-8** (Scheme 1).

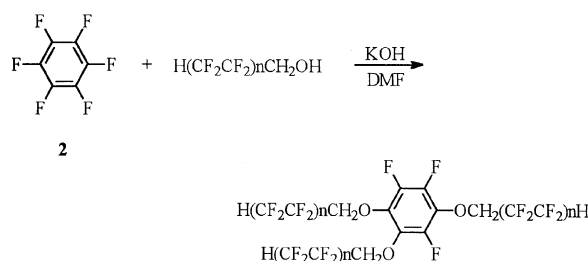
The tri-substituted products **3**, **5** and **7** were isolated as a liquid except the compound **8**, which was a crystalline solid. Octafluorotoluene (**1**) is extremely reactive towards nucleophilic attack and the trifluoromethyl group of **1** directs aromatic nucleophilic substitution into *ortho* or *para* position. Octafluorotoluene smoothly reacted at room temperature with two equivalents of the fluoroalcohol to give di-substituted products. However, the di-substituted products **4** and **6** were less reactive than **1** and required a reflux in acetonitrile to provide tri-substituted products. Thus, treatment of **4** or **6** with one more equivalent of the fluoroalcohol at reflux in acetonitrile produced the tri-substituted derivative **5** or **7**. This kind of reactivity is reasonable since an introduction of electron-donating substituents into a polyfluorinated benzene ring decreases the reaction rate of nucleophilic substitution.<sup>15</sup> The fluoroaromatic compounds **1** and **2** are soluble in acetonitrile and the reaction of **1** or **2** with sodium alkoxide proceeds at the boundary of two phases, alcohol and acetonitrile. As shown in Table 1, the partly-fluorinated alkyl aryl ethers **3-8** have been successfully synthesized by using this method.

The successful reaction of **1** with the fluoroalcohols prompted us to apply the same idea upon hexafluorobenzene (**2**) instead of **1** for the synthesis of fluorinated ethers. As a result, treatment of hexafluorobenzene with  $\alpha,\alpha,\omega$ -trihydroperfluorinated alcohols, H(CF<sub>2</sub>CF<sub>2</sub>)<sub>n</sub>CH<sub>2</sub>OH, n=1-3 in the presence of equimolar amounts of KOH in DMF has pro-



- 3**, X = Y = Z = OCH<sub>2</sub>CF<sub>2</sub>CF<sub>2</sub>H; **4**, X = Y = OCH<sub>2</sub>(CF<sub>2</sub>CF<sub>2</sub>)<sub>n</sub>H, Z = F;  
**5**, X = Y = Z = OCH<sub>2</sub>(CF<sub>2</sub>CF<sub>2</sub>)<sub>n</sub>H; **6**, X = Y = OCH<sub>2</sub>(CF<sub>2</sub>CF<sub>2</sub>)<sub>n</sub>H, Z = F;  
**7**, X = Y = Z = OCH<sub>2</sub>(CF<sub>2</sub>CF<sub>2</sub>)<sub>n</sub>H; **8**, X = Y = Z = OCH<sub>2</sub>(CF<sub>2</sub>CF<sub>2</sub>)<sub>n</sub>H;

Scheme 1



- 9**, n=1; **10**, n=2; **11**, n=3

Scheme 2

**Table 1.** The  $^1\text{H}$  and  $^{19}\text{F}$  NMR Data of the Partly-fluorinated Alkyl Aryl Ethers **3-11**

Compound	$^1\text{H}$ NMR					$^{19}\text{F}$ NMR															
	$\text{CF}_2\text{H}$	$^1J_{\text{HF}}$ ( $^2J_{\text{HF}}$ )	$\text{CH}_2\text{-}p$	$\text{CH}_2\text{-}o$	$^2J_{\text{HF}}$	$\text{CF}_2$	$\text{CF}_2$	$\text{CF}_2$	$\text{CF}_2$	$\text{CF}_2$	$\text{CF}_2$	$\text{CF}_2$	$\text{CF}_2$	$\text{CF}_2$	$^1J_{\text{FH}}$	$^3\text{F}$	$^5\text{F}$	$^6\text{F}$	$\text{CF}_3$		
<b>3</b>	5.94	53 (4)	4.33	4.27	12.3											37.6	24.0	53	17.3	17.3	108.1
<b>4</b>	6.04	52 (4)	4.77	4.59	12.8					43.1	38.9	33.7	26.4	52	16.2	9.7	23.3			107.6	
<b>5</b>	6.02	52 (4)	4.77	4.65	12.8					43.2	36.7	33.7	26.2	52	17.7	17.7				108.7	
<b>6</b>	5.97	53 (4)	4.76	4.65	12.8			43.7	42.3	40.1	39.2	33.9	26.2	52	16.0	9.5	18.2			108.7	
<b>7</b>	5.81	52 (4)	4.52	4.36	12.8			43.3	42.1	40.6	40.6	34.1	26.2	52	17.2	17.2				108.7	
<b>8</b>	6.54	51 (4)	4.82	4.61	13.0	43.5	42.3	42.3	42.3	41.0	41.0	34.6	25.8	51	18.3	18.3				108.3	
<b>9</b>	6.21	52 (5)		4.70	13.0							37.5	24.5	52	13.3	7.3	6.0				
<b>10</b>	6.60	52 (5)		4.66	13.0					40.8	36.7	34.7	26.0	52	12.6	7.2	6.1				
<b>11</b>	6.25	52 (5)		4.70	13.0			43.0	42.0	40.8	40.8	34.2	26.0	52	14.0	8.0	6.3				

**Table 2.** The Yields, Boiling Points and Analytical Data of the Partly-fluorinated Alkyl Aryl Ethers **3-11**

Compound	Yield, %	B.p. $^{\circ}\text{C}/$ Torr	Found, %			Formula	Calculated, %		
			C	H	F		C	H	F
<b>3</b>	75	120-122/1.5	34.13	1.47	56.24	$\text{C}_{16}\text{H}_9\text{F}_{17}\text{O}_3$	33.57	1.57	56.47
<b>4</b>	64	125-127/2.5	30.67	0.94	63.12	$\text{C}_{17}\text{H}_6\text{F}_{22}\text{O}_2$	30.91	0.91	63.33
<b>5</b>	73	200-202/1.5	30.44	1.06	62.73	$\text{C}_{22}\text{H}_9\text{F}_{29}\text{O}_3$	30.28	1.03	63.19
<b>6</b>	56	128-130/1.5	29.24	0.69	66.14	$\text{C}_{21}\text{H}_6\text{F}_{30}\text{O}_2$	29.30	0.70	66.28
<b>7</b>	64	182-184/0.4	28.66	0.83	66.64	$\text{C}_{28}\text{H}_9\text{F}_{41}\text{O}_3$	28.67	0.77	66.47
<b>8</b>	72	208-210/1.5	27.74	0.62	68.12	$\text{C}_{34}\text{H}_9\text{F}_{53}\text{O}_3$	27.71	0.61	68.41
<b>9</b>	85	134-135/0.4	34.31	1.58	54.12	$\text{C}_{15}\text{H}_9\text{F}_{15}\text{O}_3$	34.48	1.72	54.50
<b>10</b>	72	162-164/0.4	30.47	1.41	62.34	$\text{C}_{21}\text{H}_9\text{F}_{27}\text{O}_3$	30.66	1.09	62.41
<b>11</b>	87	198-199/0.4	28.74	0.69	66.20	$\text{C}_{27}\text{H}_9\text{F}_{39}\text{O}_3$	28.88	0.80	66.04

vided the aromatic nucleophilic substitution products **9-11** in good yields. (Scheme 2 and Table 1)

It should be underscored that hexafluorobenzene, which is much less reactive than octafluorotoluene in an aromatic nucleophilic substitution,<sup>15</sup> required a higher reaction temperature than octafluorotoluene. The reaction of **2** with three equivalents of  $\alpha,\alpha,\omega$ -trihydroperfluorinated alcohols,  $\text{H}(\text{CF}_2\text{CF}_2)_n\text{CH}_2\text{OH}$ ,  $n=1-3$  at  $100\text{ }^{\circ}\text{C}$  in the presence of KOH in DMF (or DMSO, sulfolane) for 4-6 h gave the tri-substituted benzene derivatives **9-11**. During the reaction, the first substituted group,  $\text{H}(\text{CF}_2\text{CF}_2)_n\text{CH}_2\text{O}$ , prefers to direct the second nucleophilic substitution at the *para* position rather than *ortho* position. Consequently, tri-substituted products have the substituents at 1, 2 and 4 positions.

The structure of products was confirmed by NMR, IR and elemental analysis. And,  $^1\text{H}$  NMR data of the synthesized partly-fluorinated alkyl aryl ethers revealed the characteristic signals for the protons of  $\text{CH}_2$  and  $\text{CF}_2\text{H}$  groups (Table 1).

In short, the partly-fluorinated alkyl aryl ethers **3-11** have been effectively synthesized by treatment of **1** or **2** with  $\alpha,\alpha,\omega$ -trihydroperfluorinated alcohols,  $\text{H}(\text{CF}_2\text{CF}_2)_n\text{CH}_2\text{OH}$ ,  $n=1-4$ . The partly-fluorinated ethers **3-11** might be used themselves as a lubricant, hydraulic liquid or precursors for the synthesis of perfluorinated ethers.

## Experimental Section

The  $^1\text{H}$  and  $^{19}\text{F}$  NMR spectra were taken with a Bruker WP 200 SY spectrometer on the frequency of 200.133 and 188.291 MHz with an internal standard TMS or  $\text{C}_6\text{F}_6$ . Infrared spectra were taken with a Bruker IFS66 FT-IR spectrometer (5% in  $\text{CCl}_4$ ): 1052, 1114-1127 (C-O), 1182-1204 (C-F), 1282, 1329 (C-O), 1480-1490 ( $\text{C}=\text{C}_{\text{ar}}$ ), 2930 (C-H)  $\text{cm}^{-1}$ . Reaction mixtures were analyzed with an LKB-2091 mass spectrometer. All the reactions and individual products were checked by  $^{19}\text{F}$  NMR and GC. Reaction mixtures were analyzed by GC using an LCM 72 chromatograph (15% SE-30, SKTF-803: QF-1, Chromosorb W, column 4 m, diameter of 4 mm) with a thermal conductivity detector.

**Typical procedure for the synthesis of partly-fluorinated alkyl aryl ethers.** To a solution of octafluorotoluene (11.80 g, 0.050 mol) and KOH (8.42 g, 0.15 mol) in MeCN (30 mL) at  $0\text{ }^{\circ}\text{C}$  was added dropwise 2,2,3,3-tetrafluoro-1-propanol (19.81 g, 0.15 mol). The resulting solution was stirred at room temperature for 1 h and then heated at reflux for 5 h. The reaction mixture was diluted with water (250 mL) and neutralized with 5% aqueous  $\text{H}_2\text{SO}_4$ . The organic phase was separated and washed with water ( $2 \times 50$  mL), brine (50 mL) and dried over  $\text{MgSO}_4$ . Distillation of the crude product under reduced pressure gave **3** (21.4 g, 75% yield) as a colorless liquid. The reaction results are

summarized in Table 2.

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