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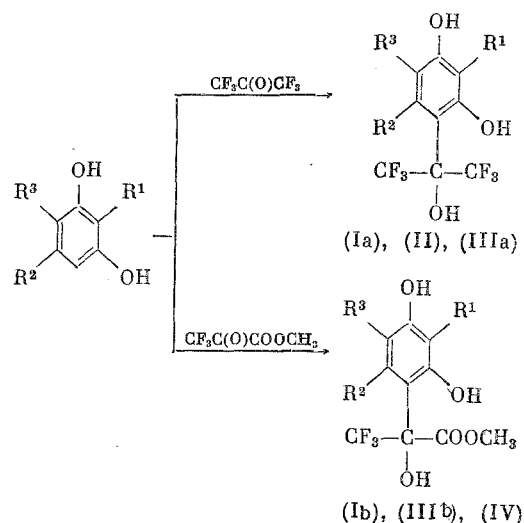
REACTIONS OF POLYFLUOROCARBONYL COMPOUNDS WITH POLYPHENOLS

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The general features of the reactions of phenols with hexafluoro-[1-7] and tetrafluoro-dichloroacetone [3] in the presence of Lewis acids and sulfonic acids are well known. We here consider the uncatalyzed reaction of hexafluoroacetone and MeOCCOCF₃ with di- and trihydroxybenzenes.

It has been found that resorcinol, phloroglucinol, hydroxyhydroquinone, and pyrogallol react in ether, MeNO₂, and benzene in the absence of a catalyst at temperatures as low as 20°C with hexafluoroacetone and methyl trifluoropyruvate to give C-alkylation products (Ia, b), (II), (IIIa, b), and (IV). Only pyrocatechol and hydroquinone failed to react even at 100°C.



R¹=R²=R³=H (Ia,b); R¹=R³=H, R²=OH (II); R¹=OH, R²=R³=H (IIIa,b);
R¹=R²=H, R³=OH (IV).

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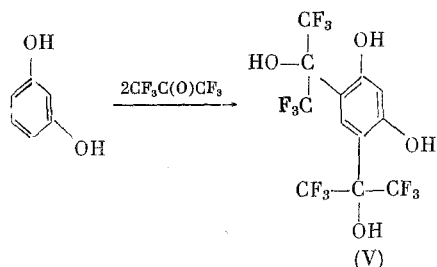
TABLE 1. Conditions of Formation, Yields, and Properties of (Ia, b), (II), (IIIa, b), (IV), (Vla-c), and (VIIa-d)

Compound	Solvent	Reaction time, h (reaction temp., deg C)	Yield, %	mp, deg C (solvent)	R _f (acetone: CCl ₄)	Found/calculated, %			Empirical formula
						C	H	F	
(Ia)	Benzene	2(20)	95	142-144 (benzene)	0.54 (1:1)	39.22 39.13	2.10 2.18	41.32 41.30	C ₉ H ₆ F ₆ O ₃
(Ib)	Nitro- methane	8(20)	99	160-162 (nitromethane)	0.42 (1:1)	45.53 45.41	3.09 3.38	20.93 21.43	C ₁₀ H ₉ F ₃ O ₃
(II)	Ether	8(20)	88	214-216 (benzene)	0.50 (1:1)	37.35 36.97	2.14 2.06	38.63 39.04	C ₉ H ₆ F ₆ O ₄
(IIIa)	Benzene	1(80)	90	116-118 (benzene)	0.44 (1:1)	37.41 36.97	1.76 2.06	38.90 39.04	C ₉ H ₆ F ₆ O ₄
(IIIb)	»	1(80)	98	127-129 (benzene)	0.37 (1:1)	43.03 42.55	2.88 3.19	20.02 20.21	C ₁₀ H ₉ F ₃ O ₃
(IV)	»	1(80)	95	178-180 (nitromethane)	0.38 (1:1)	42.60 42.55	3.24 3.19	19.73 20.21	C ₁₀ H ₉ F ₃ O ₃
(VIa)	»	8(20)	98	81-83 (hexane)	0.41 (1:3)	41.41 41.38	2.71 2.76	39.41 39.31	C ₁₀ H ₉ F ₆ O ₃
(VIb) *	»	8(20)	96	—	0.47 (1:1)	43.81 43.42	3.27 3.25	39.41 39.30	C ₁₁ H ₁₀ F ₆ O ₃
(VIc)	»	8(20)	95	47-49 (hexane)	0.55 (1:3)	47.32 46.99	3.95 4.22	34.05 34.34	C ₁₃ H ₁₄ F ₆ O ₃
(VIIa)	—	24(20)	99	63-64 (pentane)	0.61 (1:3)	48.46 48.65	4.72 5.07	19.04 19.25	C ₁₂ H ₁₃ F ₃ O ₅
(VIIb)	—	24(20)	99	93-95 (benzene)	0.38 (1:3)	52.26 52.17	5.39 5.28	17.35 17.70	C ₁₄ H ₁₇ F ₃ O ₅
(VIIc)	—	124(20)	99	62-64 (pentane)	0.60 (1:3)	56.81 57.14	6.54 6.61	14.85 15.08	C ₁₈ H ₂₃ F ₃ O ₅
(VIId)	—	124(20)	99	35-37 (hexane)	0.69 (1:1)	43.22 43.42	3.07 3.29	37.53 37.50	C ₁₁ H ₁₀ F ₆ O ₅

*Bp 107-110°C (2 mm), n_D²⁰ 1.4525.

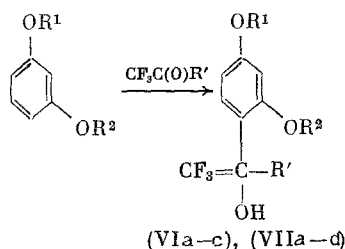
Using equimolar amounts of the reactants, products (I)-(IV) were obtained in high yields (>90%) only in benzene and MeNO₂, which are not able to specifically solvate phenolic compounds. The reactions proceed fairly quickly to completion at 20°C, only the sparingly soluble trihydroxybenzenes requiring brief heating to 80°C. In ether, using equimolar amounts of the reactants, the yields of C-alkylation products did not exceed 60%, apparently owing to the facile O-alkylation of solvated phenolic compounds by polyfluoroketones. However, when a twofold excess of the polyfluorocarbonyl compound was used in ether at 20°C, the trihydroxybenzenes gave products (II)-(IV) in ~90% yields.

It is noteworthy that resorcinol, unlike the trihydroxybenzenes, reacts readily with excess hexafluoroacetone to give the double C-alkylation product (V).



Methyl trifluoropyruvate does not give 2:1 adducts with resorcinol or trihydroxybenzenes.

In addition to the polyphenols themselves, their mono- and di-ethers also undergo C-alkylation by polyfluorocarbonyl compounds. For example, meta-alkoxyphenols react readily (20°C, 8 h, benzene) with hexafluoroacetone, albeit less readily than resorcinol, to give 2-(α-hydroxyhexafluoroiso-propyl)-5-alkoxyphenols (VIa-c) in yields of >95%. 1,3-Dialkoxybenzenes react much less readily (20°C, 1-6 days) with methyl trifluoropyruvate, to give quantitative yields of the C-alkylation products (VIIa-d).



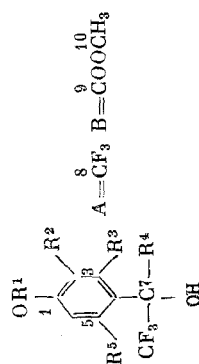
R¹=CH₃, R²=H, R'=CF₃ (VIa); R¹=C₂H₅, R²=H, R'=CF₃ (VIb); R¹=C₄H₉, R²=H, R'=CF₃ (VIc); R¹=R²=CH₃, R'=COOCH₃ (VIIa); R¹=R²=C₂H₅, R'=COOCH₃ (VIIb); R¹=R²=C₄H₉, R'=COOCH₃ (VIIc); R¹=R²=CH₃, R'=CF₃ (VIId).

In contrast to resorcinol ethers, the monomethyl ethers of pyrocatechol and hydroquinone fail to react with polyfluoroketones even at 100°C.

These results show that under mild, noncatalyzed conditions only polyphenols and their ethers containing at least two hydroxy or alkoxy groups with identical orienting effects undergo C-alkylation by polyfluorocarbonyl compounds. The C-alkylation of these compounds is a regiospecific reaction, the substituents having only ortho-para orientating effects. Monoethers of resorcinol are alkylated exclusively in the ortho-position to the OH group.

In order to assess the influence of the concerted orientation of other substituents of the first type on the conditions of C-alkylation of phenols by polyfluoroketones, the reactions of hexafluoroacetone with meta-substituted alkyl-, halo- and aminophenols were examined. It was found that meta-alkyl and meta-halophenols did not undergo the noncatalyzed reaction with hexafluoroacetone, even at 100°C. However, with N-(p-tolyl)-m-aminophenol in benzene, the reaction proceeded even more readily than with trihydroxybenzenes or resorcinol, giving the double C-alkylation product (VIII) even at 20°C.

TABLE 2. NMR Spectra of (Ia, b), (II), (IIIa, b), (IV), (VIa, b), and (VIIa-d)

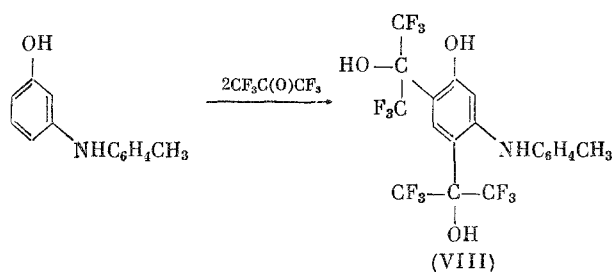


Com- pound	R	^{13}C NMR, δ , ppm										$^{13}\text{C-F}$	^{19}F
		1	2	3	4	5	6	7	8	9	10		
(Ia)	$\text{R}^1=\text{R}^2=\text{R}^3=\text{H}$, $\text{R}^3=\text{OH}$, $\text{R}^4=\text{A}$	158.90	103.30	156.50	104.70	128.30	107.50	78.70	122.22	—	—	285.00	30.45
(Ib)	$\text{R}^1=\text{R}^2=\text{R}^3=\text{H}$, $\text{R}^3=\text{OH}$, $\text{R}^4=\text{B}$	160.21	104.30	157.70	112.70	130.04	107.90	79.00	124.94	—	53.20	286.60	29.02
(II)	$\text{R}^1=\text{R}^2=\text{H}$, $\text{R}^3=\text{R}^4=\text{OH}$, $\text{R}^4=\text{A}$	158.65	95.35	157.79	94.66	156.78	95.35	79.89	122.46	—	—	287.50	30.50
(IIIa)	$\text{R}^1=\text{R}^2=\text{H}$, $\text{R}^3=\text{R}^4=\text{OH}$, $\text{R}^4=\text{A}$	144.89	146.01	132.52	105.44	117.34	106.89	78.26	122.19	—	—	286.50	30.43
(IIIb)	$\text{R}^1=\text{R}^2=\text{H}$, $\text{R}^3=\text{R}^4=\text{OH}$, $\text{R}^4=\text{B}$	143.97	145.45	131.83	111.32	117.31	105.71	77.00	122.91	—	—	283.50	30.75
(IV)	$\text{R}^1=\text{R}^2=\text{H}$, $\text{R}^3=\text{R}^4=\text{OH}$, $\text{R}^4=\text{B}$	149.86	147.72	104.91	138.58	111.52	115.51	79.45	124.78	167.31	51.36	284.00	30.67
(VIa)	$\text{R}^1=\text{CH}_3$, $\text{R}^2=\text{R}^3=\text{H}$, $\text{R}^3=\text{OH}$, $\text{R}^4=\text{A}$	160.91	102.02	156.46	105.50	128.13	105.69	78.34	122.15	—	—	286.00	30.59
(VIb)	$\text{R}^1=\text{C}_2\text{H}_5$, $\text{R}^2=\text{R}^3=\text{H}$, $\text{R}^3=\text{OH}$, $\text{R}^4=\text{A}$	161.00	102.03	156.54	105.55	128.13	106.07	78.34	122.18	—	—	286.80	30.59
(VIa)	$\text{R}^1=\text{CH}_3$, $\text{R}^2=\text{R}^3=\text{H}$, $\text{R}^3=\text{OCH}_3$, $\text{R}^4=\text{B}$	160.84	97.77	157.17	115.45	128.04	103.98	74.40	122.82	167.66	50.96	284.00	30.25
(VIIb)	$\text{R}^1=\text{C}_2\text{H}_5$, $\text{R}^2=\text{R}^3=\text{H}$, $\text{R}^3=\text{OC}_2\text{H}_5$, $\text{R}^4=\text{B}$	160.01	98.54	156.36	115.04	127.94	104.16	75.85	122.83	167.55	50.85	285.00	30.25
(VIIc)	$\text{R}^1=\text{C}_4\text{H}_9$, $\text{R}^2=\text{R}^3=\text{H}$, $\text{R}^3=\text{OC}_4\text{H}_9$, $\text{R}^4=\text{B}$	160.23	98.41	156.58	114.87	127.95	104.06	75.26	122.83	167.45	50.85	283.50	30.47
(VIIa)	$\text{R}^1=\text{CH}_3$, $\text{R}^2=\text{R}^3=\text{H}$, $\text{R}^3=\text{OCH}_3$, $\text{R}^4=\text{A}$	161.00	99.10	158.80	108.20	128.10	105.40	78.45	122.16	—	—	285.50	30.16

TABLE 3. PMR Spectra of (Ib), (II), (IIIa), (VIa, c), and (VIIa, b, d)*

Compound	δ , ppm/(J, Hz)				
	2	5	6	OH	OCH ₃
(Ib)	6.48 s	6.81 d (8,9)	6.40 d	8.43 s 8.13 s 7.60 s	3.68 s
(II)	6.09 d	— (2,7)	6.03 d	10.25 s 9.10 s 8.70 s 8.60 s	—
(IIIa)	—	6.89 hept (J _{H-F} 1,7) (9,0)	6.59 d	8.20 9.00 br.s	—
(VIa)	6.55 s	7.47 d (8,5)	6.61 q (2,5)	10.30 br.s 8.30 br. s	3.76 s
(VIc)	6.50 s	7.30 d (9,0)	6.40 d	—	—
(VIIa)	6.60 s	7.50 d (9,1)	6.65 d	7.60s	3.78s 3.73s 3.70s
(VIIb)	6.65 s	7.45 d (8,5)	6.58 d	7.58 s	3.70s
(VIIc)	6.70 s	7.65 d (9,0)	6.65 d	8.18 s	3.78s

*The spectra of (VIIa, b, d) were obtained in DMSO-d₆, the remainder in acetone-d₆.



It appears that only meta-substituted phenols, the substituent in which has a sufficiently high electromeric effect, are capable of undergoing mild, noncatalyzed C-alkylation by polyfluorocarbonyl compounds.

EXPERIMENTAL

¹H, ¹³C, and ¹⁹F NMR spectra of the compounds obtained were recorded in acetone, acetone-d₆, and DMSO-d₆ at 20°C on a Bruker R-200SY spectrometer at operating frequencies of 200.12, 50.31, and 188.30 MHz respectively. Chemical shifts (δ , ppm) were measured relative to TMS (¹H, ¹³C, internal standard) or CF₃COOH (¹⁹F, external standard). The R_f values of the products were measured on Silufol UV-254 plates (Kavalier, Czech SR) in the system acetone-CCl₄ (1:1 and 1:3). The compounds were visualized by their absorption of UV light.

1,3-Dihydroxy-4-(α -hydroxyhexafluoroisopropyl)benzene (Ia). In a glass ampul were placed 20 ml of dry benzene and 2.2 g of finely-ground resorcinol, followed at -70°C by 4.0 g of hexafluoroacetone. The ampul was sealed, then warmed to 20°C and shaken for 2 h. After cooling, the ampul was opened, and the product filtered off and recrystallized. The yield and properties of (Ia) are given in Tables 1 and 2. Compounds (II), (IIIa), (IVa-c), and (VIId) were obtained similarly (Tables 1-3).

1,3-Dihydroxy-4-(α -hydroxy- α -methoxycarbonyltrifluoroethyl)benzene (Ib). A mixture of 1.1 g of resorcinol and 1.7 g of methyl trifluoropyruvate in 8 ml of nitromethane was kept at 20°C for 8 h, the mixture evaporated under reduced pressure, and the residue crystallized. The yield and properties of (Ib) are given in Tables 1-3. Compounds (IIIb), (IV), and (VIIa-c) were obtained similarly.

1,5-Dihydroxy-2,4-di-(α -hydroxyhexafluoroisopropyl)benzene (V). In a glass ampul were placed 15 ml of benzene and 1.1 g of resorcinol, cooled, 4.0 g of hexafluoroacetone condensed into the mixture, the ampul sealed, warmed to 20°C, heated rapidly to 80°C, kept for 0.5 h, and cooled. The ampul was opened, and the product recrystallized from benzene to give 3.98 g (90%) of (V), mp 163-165°C, R_f 0.50 (acetone-CCl₄, 1:1). ¹³C NMR spectrum (acetone): 157.90 (C¹, C⁵), 128.73 (C³), 121.74 (CF₃, J_{C-F} = 264 Hz), 106.20 (C⁶), 78.20 (C⁷, J_{C-F} = 30.27 Hz). PMR spectrum (acetone-d₆): 7.69 s (1H, H³), 6.64 s (1H, H⁶). ¹⁹F NMR spectrum (acetone-d₆): 8.1 s. Found: C 32.61; H 1.36; F 51.26%. C₁₂H₆F₁₂O₄. Calculated: C 32.58; H 1.36; F 51.58%.

2,4-Di-(α -hydroxyhexafluoroisopropyl)-5-[N-(p-tolyl)amino]phenol (VIII). A mixture of 1.99 g of N-(p-tolyl)-m-aminophenol, 4.0 g of hexafluoroacetone, and 15 ml of benzene was kept in a sealed ampul at 20°C for 10 h. The ampul was then cooled, opened, and the product crystallized from CCl₄ to give 4.25 g (80%) of (VIII), mp 123-125°C, R_f 0.43 (acetone-CCl₄, 1:1). ¹³C NMR spectrum (acetone): 156.97 (C¹), 148.60 (C⁵), 128.40 (C³), 122.32 and 122.12 (CF₃, J_{C-F} = 287 Hz), 106.19 (C⁴), 104.17 (C⁶), 78.70 and 78.90 (C-CF₃, J_{C-F} = 30.0 Hz). Found: C 43.03; H 2.50; N 2.69%. C₁₉H₁₃F₁₂NO₃. Calculated: C 42.94; H 2.45; N 2.64%.

CONCLUSIONS

1. Resorcinol and trihydroxybenzenes react with hexafluoroacetone and methyl trifluoropyruvate in the absence of a catalyst in nonpolar media to give nearly quantitative yields of the mono-C-alkylation products. The reaction is regiospecific, at the site of concerted ortho-para orientation by the OH groups.

2. Of the mono-hydroxybenzenes, only those compounds with meta-substituents in which the substituent has a large electromeric effect undergo C-alkylation with polyfluorocarbonyl compounds.

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