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CHARACTERISTIC FEATURES OF REACTIONS OF PHENOLATE IONS WITH POLYFLUOROCARBONYL COMPOUNDS

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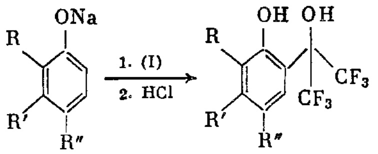
It has been shown previously [1, 2] that hexafluoroacetone (I) and methyl trifluoropyruvate (II) C-alkylate sodium phenolate, alkyl-, and dialkylphenolates in nonpolar solvents under much milder conditions than with free phenols, which conforms with the increase in the C-nucleopholicity on transition from phenol to phenolate systems. The characteristic feature of these reactions is their regiospecificity, manifesting itself in the exclusive formation of o-alkylation products and in the absence of ortho- and meta-substituents, in the formation also of ortho-ortho-dialkylation products. In the present work, we discuss the influence of the structure of the ambidentate phenolate ion on the conditions and direction of its reactions with (I) and (II), and also give the preliminary results of study of the influence of a counterion and aprotic solvents on these transformations.

Mono-substituted sodium phenolates with electron-acceptor substituents at the o-, m-, and p-positions also react with ketone (I) in Freon-113 under fairly mild conditions exclusively giving the o-alkylation products (III)-(VII) in a 72-96% yield



(III)—(VII)

R = R' = H, R" = Cl (III); R = Cl, R' = R" = H (IV); R = Br, R' = R" = H (V); R = R" = H, R' = F (VI); R = COOCH$_3$, R' = R" = H (VII).

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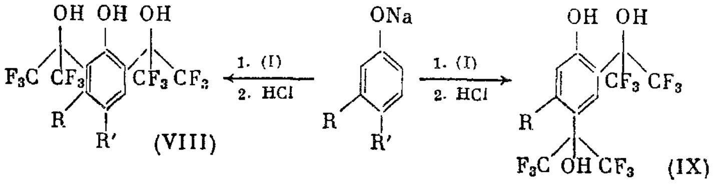
TABLE 1. Influence of Solvent and Metal Ion on Direction of Alkylation Reaction of a Phenolate Ion

Metal ion	Solvent	
	Freon-113 (yield, %)	DMF (yield, %)
Li	o-Adduct (64)	p-Adduct (65)
Na	» (71)	» (75)
K	p-Adduct (31)	» (70)

Thus, phenol (VI) is formed already on mixing the reagents, while compounds (III)-(V), (VII) are formed only after on moderate heating (80-90°C, 0.5-1.0 h). Only second order substituents, which strongly inactivate the free o-position, hinder the occurrence of such a reaction. Thus, Na-derivatives of m-nitrophenol, methyl ester of p-hydroxybenzoic acid and vannilin do not react with ketone (I) even at 100°C.

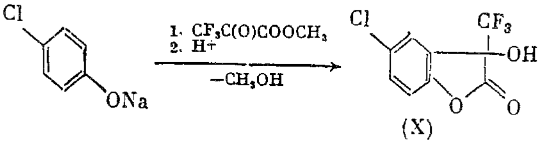
In the presence of excess ketone (I), Na m- and p-halophenolates undergo a double C-alkylation. Thus, sodium p-bromophenolate forms an o-o-dialkylation product (VIII), while m-fluorophenolate forms an o-p-dialkylation product (IX) in yields of 70.3 and 61%, respectively.



R = H, R = Br (VIII); R = F (IX).

Sodium o-bromophenolate and sodium methyl salicylate do not undergo the di-C-alkylation with ketone (I) under the conditions at which the synthesis of their monosubstituted adducts was carried out.

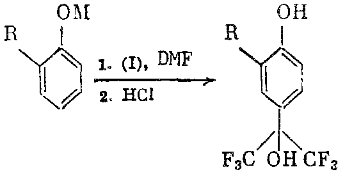
Ketoester (II) C-alkylates Na p-chlorophenolate as readily as (I); the product formed was isolated in the form of benzofuranone (X) in 70% yield after acid treatment



(X)

In the study of the influence of the counterion on the conditions and direction of the substitution by ketone (I), it was shown that Li and Na phenolates become C-alkylated in Freon-113 with equal ease (80°C, 30 min) with the formation of an o-alkylation product in 64 and 71% yields, respectively (Table 1). Potassium phenolate enters reaction with ketone (I) under more rigorous conditions, forming a p-alkylation product (XI) only. At 100°C, after 2 h, the yield of (XI) is not more than 31%, which is probably due to the low solubility of K phenolate in Freon-113. In fact, in DMF at 80°C, after 1 h, the p-alkylation product of K phenolate is obtained in >70% yield. Lithium and sodium salts of phenol in DMF react with ketone (I) similarly to K phenolate and form the same p-adduct (XI).

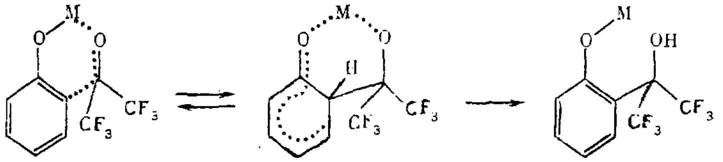
The solvent also exerts a similar influence on the direction of the C-alkylation reaction by ketone (I) when o-chlorophenolates are used, whereby in DMF, the p-adduct (XII) was obtained in good yield



(XI), (XII)

R = H (XI); R = Cl (XII). M = Li$^+$, Na$^+$, K$^+$.

The regiospecific o-C-alkylation of Li and Na phenolates in nonpolar aprotic solvents possibly occurs as a result of the formation of ordered transition states due to chelate-formation effects.



The suppression of chelate formation when a counterion (K^+) is used, which is less susceptible to undergoing this kind of reaction [3], or as a result of effective solvation of the cation by the solvent, leads to the formation of p-adducts.

EXPERIMENTAL

The ^{13}C and ^{1}H NMR spectra of the compounds synthesized were obtained on Bruker R-200-SY spectrometer with working frequencies of 50.31 and 200.12 MHz, respectively, while the ^{19}F NMR spectra were run on a Perkin-Elmer R-32 spectrometer with a working frequency of 84.6 MHz. The chemical shifts were determined relative to TMS (^{13}C, ^{1}H, external standard) and CF_3COOH (^{19}F, internal standard). The R_f values are given for Silufol UV-254 plates in an acetone:CCl_4 system (1:3). The compounds were detected in UV light. The conditions of formation and the properties of the compounds are given in Table 2, and the spectral characteristics in Table 3.

2-(α-Hydroxyhexafluoroisopropyl)-4-chlorophenol (III). A 11.5-g portion of dry, finely ground Na p-chlorophenolate and 40 ml of anhydrous Freon-113 were placed in a glass ampul and 15.0 g of ketone (I) was introduced into the ampul by condensation at 78°C. The ampul was sealed, heated with periodic shaking at 80°C for 1 h, and then cooled again (−78°C), opened, and the contents were neutralized with an excess of 10% HCl. The organic layer was separated, dried over Na_2SO_4, filtered, and the filtrate was evaporated. The crude product (23.0 g) was crystallized from hexane. Yield, 18.0 g of phenol (III), in the form of white crystals. ^{13}C NMR spectrum (δ, ppm, acetone): 154.15 (C^1), 130.44 (C^5), 126.95 (C^3), 123.88 (C^4), 121.85 (CF_3, J_{C-F} = 284.50 Hz), 118.60 (C^6), 115.36 (C^2), 78.19 [$\underline{C}(CF_3)_2OH$, J_{C-F} = 31.0 Hz].

2-(α-Hydroxyhexafluoroisopropyl)-6-chlorophenol (IV). In a similar way as for (III), from 6.0 g of Na o-chlorophenolate and 8.3 g of ketone (I) in 30 ml Freon-113, 10.6 g of white crystals (from pentane) were obtained. ^{13}C NMR spectrum (δ, ppm, acetone): 151.57 (C^1), 130.92 (C^5), 127.87 (C^3), 122.17 (C^6), 121.83 (CF_3, J_{C-F} = 286.0 Hz), 119.65 (C^4), 115.12 (C^2), 78.85 [$\underline{C}(CF_3)_2OH$, J_{C-F} = 30.5 Hz].

2-(α-Hydroxyhexafluoroisopropyl)-6-bromophenol (V). In the same way as for (III), from 5.88 g of Na o-bromophenolate and 6.64 g of ketone (I) in 20 ml of Freon-113, a crude product (10.0 g) was obtained, which was crystallized from pentane at −60 to −50°C. The yield of (V) was 7.4 g.

2-(α-Hydroxyhexafluoroisopropyl)-5-fluorophenol (VI). In the same way as for (III), from 6.7 of Na m-fluorophenolate and 9.0 g of ketone (I) in 30 ml of Freon-113, after crystallization from hexane, 13.34 g of (VI) were obtained.

Methyl 2-(α-Hydroxyhexafluoroisopropyl)salicylate (VII). In the same way as for (III), from 8.75 g of Na methyl salicylate and 10.0 g of ketone (I) in 45 ml of Freon-113, a crude product (14.0 g) was obtained, which was crystallized from hexane. The yield of (VII) was 12.7 g. ^{13}C NMR spectrum (δ, ppm, acetone): 169.67 ($\underline{C}OOCH_3$), 158.84 (C^1), 134.25 and 131.42 (C^3, C^5), 121.98 (CF_3, J_{C-F} = 284.0 Hz), 118.66 (C^6), 116.23 (C^4), 112.65 (C^2), 78.07 [$\underline{C}(CF_3)_2OH$, J_{C-F} = 31.04 Hz], 51.63 (OCH_3).

2,6-Bis-(α-hydroxyhexafluoroisopropyl)-4-bromophenol (VIII). Under the conditions of the synthesis of (III), from 3.90 g of Na p-bromophenolate and 10.0 g of ketone (I) in 15 ml of Freon-113, after the crystallization of the crude product from heptane, 7.10 g of (VIII) were obtained.

2,4-Bis-(α-hydroxyhexafluoroisopropyl)-5-fluorophenol (IX). In a similar way as for (III), from 2.68 g of Na m-fluorophenolate and 7.0 g of ketone (I) in 20 ml of Freon-113, after crystallization of the crude product (7.0 g) from hexane, 5.42 g of (IX) were obtained.

TABLE 2. Conditions of Formation, Yield and Properties of Compounds Obtained

Compound	Time, h	Yield, %	Mp, °C (solvent)	R_f	Found/Calculated, %			Empirical formula
					C	H	F	
(III)	1.0	80.0	117–119 (heptane)	0.60	36,96 36,67	1.77 1.70	39,02 38.71	$C_9H_5F_6ClO_2$
(IV)	1,0	90,3	42–45 (pentane)	0.50	36,72 36.67	1.83 1.70	38.61 38.71	$C_9H_5F_6ClO_2$
(V)	1,5	72,4	40–42 (pentane)	0,50	31.78 31.86	1.33 1.48	33.60 33.63	$C_9H_5BrF_6O_2$
(VI)	0,5	96,0	100–103 (hexane)	0.47	38.70 38.85	1.70 1.80	47.98 47.84	$C_9H_5F_7O_2$
(VII)	1,0	79,4	54–56 (hexane)	0.64	41.50 41,51	2.13 2.52	36.11 35.85	$C_{11}H_8F_6O_4$
(VIII)	2,0	70,3	148–149 (heptane)	0,50	28.35 28,51	1.05 0.99	44.98 45.15	$C_{12}H_5F_{12}BrO_3$
(IX)	1,0	61,0	105–108 (hexane)	0,29	32.35 32.43	0.91 1.13	55.62 55,63	$C_{12}H_5F_{13}O_3$
(X)	1.0	70,0	93–95 (benzene)	0.50	42.50 42,77	1.64 1.58	22.41 22,57	$C_9H_4F_3ClO_2$
(XII)	2,0	67,9	67–69 (Freon-113)	0,56	36.39 36,67	1.56 1.70	38.56 38.71	$C_9H_5F_6ClO_2$

TABLE 3. ^1H and ^{19}F NMR Spectra of Compounds Obtained

Compound	Chemical shifts (δ, ppm, J, Hz)*					
	H^3	H^4	H^5	H^6	OH	^{19}F
(III)	7,45 br.s	–	7,35 d.d	7,05 d	9,70–8.60 br.s	–3,11 s
		(2,5)				
			(9,0)			
(IV)	7,70 d	–	7.45 d.d	7.0 d	7.85 s 6.60 s	–2,66 s
		(2.5)				
			(9,0)			
(V)	7.51 d.d	6,85 d.d	7.42 br.d	–	6.80 s 6.35 s	–2.80 s
	(8.0)					
		(8,1)				
		(1,4)				
(VI)	7.50 d.d hept $J_{H-F}=7.5$ $J_{H-F}=0,5$	6.70 m $J_{H-F}=6,0$	–	6.75 d $J_{H-F}=9.0$	10.0–8.0 br.s	
	(7.5)					
(VII) **	8.08 d.hept $J_{H-F}=0,5$	7,20 t	7,93 d	–	–	–3,5 s
	(7,8)					
		(7,7)				
(VIII)	7.75 s	–	7,75 s	–	–	–3.33 s
(IX)	7.93 br.d $J_{H-F}=8,5$	–	–	6.61 d $J_{H-F}=13.0$	8.11 s	–3.40 d (CF_3, J_{F-F} 20,7) –3.11 s 26.3 d (F)
(XII)	7.70 d	–	7,45 d.d	7.00 d	7,80 s 6.65 s	–2,66 s
		(2,5)				
			(9,0)			

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*The ^1H and ^{19}F NMR spectra of compounds (III), (IV), (VII)-(IX) were run in d-acetone, (V) in CCl_4, (XII) in deuterochloroform.

**In the PMR spectrum a signal (δ 4.0 ppm, s) of the CH_3O group was observed.

3-Hydroxy-3-trifluoromethyl-5-chloro-2(3H)benzo[b]furanone (X). A mixture of 4.50 g of Na p-chlorophenolate and 5.1 g of ketoester (II) in 25 ml of absolute benzene was boiled for 1 h, was then cooled, and neutralized with 20 ml of 10% HCl. The organic layer was separated, dried over $CaCl_2$, and the solvent was evaporated in vacuo. The residue (8.1 g) was boiled for 3 h in 15 ml of glacial acetic acid, the acid was distilled off, and the product was recrystallized from hexane. Yield, 5.33 g of (X). ^{13}C NMR spectrum (δ, ppm, acetone): 167.69 (C^2), 151.52 (C^7), 131.91 (C^6), 129.02 (C^5), 124.95 (C^4), 122.96 (C^3), 121.42 (CF_3, J_{C-F} = 281.5 Hz), 112.19 (C^7), 73.40 (C^3, J_{C-F} = 30.80 Hz). PMR spectrum (δ, ppm, d-acetone): 7.73 s (1H, H^4), 7.72 d (1H, H^6, J_{H-H^7} = 8.0 Hz), 7.45 s (1H, OH), 7.35 d (1H, H^7, J_{H-H^6} = 8.0 Hz). ^{19}F NMR spectrum (δ, ppm, d-acetone): 1.5 s.

4(α-Hydroxyhexafluoroisopropyl)phenol (XI). a) In a similar way as for (III), from 3.96 g of K phenolate and 5.0 g of ketone (I) in 20 ml of Freon-113, 2.4 g of (XI) were obtained, mp 126-128°C [4].

b) In a similar way as for (III), from 5.0 g of ketone (I) and 2.97 g of Li phenolate, or 3.48 g of Na phenolate, or 3.96 g of K phenolate in 20 ml of anhydrous DMF, 5.1, 5.9, and 5.5 g, respectively, of (XI) were obtained, mp 125-128°C (from hexane).

2-Chloro-4-(α-hydroxyhexafluoroisopropyl)phenol (XII). In a similar way as for (III), 7.5 g of Na o-chlorophenolate were reacted with 10.0 g of ketone (I) in 50 ml of anhydrous DMF. The reaction mixture was then stirred for 30 min with 200 ml of 5% HCl. The product was extracted with CH_2Cl_2 (3 × 25 ml). The extract was washed with 30 ml of 40% H_2SO_4, dried over Na_2SO_4, the solvent was evaporated, and the residue was crystallized from hexane. The yield of (XII) was 10.0 g.

CONCLUSIONS

1. Phenolates containing electron-acceptor substituents in the aromatic ring are regiospecifically C-alkylated by hexafluoroacetone and methyl trifluoropyruvate to form monoalkylation products, and in the presence of an excess of hexafluoroacetone form dialkylation products.

2. In Freon-113, Li and Na phenolates are alkylated by hexafluoroacetone in the o-position, and K phenolates in the p-position; in DMF, irrespective of the counterion, the phenolates form p-alkylation products with hexafluoroacetone. The regiospecific o-alkylation of Li and Na phenolates in nonpolar media, is possibly explained by chelate formation.

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