REACTIONS OF HIGHLY ELECTROPHILIC POLYFLUOROCARBONYL COMPOUNDS WITH PRIMARY ARYLAMINES

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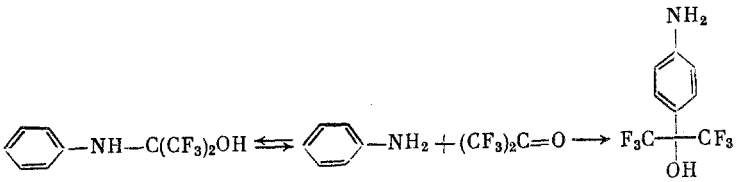
C-Hydroxyalkylation of primary arylamines by highly electrophilic polyfluorocarbonyl compounds results from the direct reaction of the initial reagents and is competitively inhibited by equilibrium N-hydroxyalkylation. The presence of steric hindrances to the formation of N-hydroxyalkylation products and an increase in the ring C-nucleophilicity facilitate the C-hydroxyalkylation reaction.

Aniline reacts vigorously with highly electrophilic polyfluoroketones to form hydrolytically unstable N-alkylation products – geminal aminohydroxy compounds [1-3]. Under drastic conditions (170-200°C), hexafluoroacetone (I) reacts with anilines, N-alkyl-N,N-dialkylanilines, and α-naphthylamine to form aromatic ring C-hydroxyalkylation products [1, 4], which are also formed by boiling anilines with hexafluoroacetone hydrate [5]. It was shown [6-9] that secondary and tertiary arylamines undergo C-hydroxyalkylation by ketone (I), as well as by trifluoropyroracemic acid methyl ester (II), at temperatures as low as 20°C. Primary arylamines react with ketoester (II) to form 3-hydroxy-2-oxo-3-(trifluoromethyl)indolines [3].

In the present work we further refine the reactivity of highly electrophilic polyfluorocarbonyl compounds with respect to primary arylamines.

Aniline reacts vigorously with compound (I) in $MeNO_2$ at −60 to 20°C in complete accordance with the data in [1] to form N-alkylation product (III), which is converted to 4-(1-hydroxy-1-trifluoromethyl-2,2,2-trifluoroethyl)aniline (IV) at the low temperature of 20°C (4 months, 40% yield). When the temperature was raised to 60°C, the C^4-hydroxyalkylation product was obtained after 24 h in a yield of 55%; the reaction was accompanied by tarring. The isomerization of (III) to (IV) appears to be an intermolecular process. The formation of compound (IV) is preceded by the dissociation of (III) to the initial reagents, whose reaction affords N- or C-alkylation products. The reaction conditions and yield of compound (IV) are practically independent of excess ketone (I) in the reaction mass, which excludes the possibility that adduct (III) is the C-alkylation substrate.



(III) (I) (IV)

In a special investigation of the reaction of compound (III) with the highly reactive ketone (I) acceptor, N,N-dimethylaniline [6], the only new product was N,N-dimethyl-4-(1-hydroxy-1-trifluoromethyl-2,2,2-trifluoroethyl)aniline (V). The rate of formation of the latter (30.8% after 40 h at 80°C) is comparable to the isomerization rate of compound (III) to compound (IV).

*Deceased.

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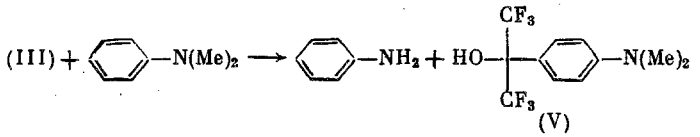
TABLE 1. Reaction Conditions and Yields for Products (IV)-(XX)

Compound	Reaction products	Time, h	Solvent	T, °C	Reagents, ratio	Yield %
(IV)	4-(1-Hydroxy-1-trifluoromethyl-2,2,2-trifluoroethyl)aniline	4 months	$MeNO_2$	20	Aniline—(I), 1:1	40
(V)	N,N-Dimethyl-4-(1-hydroxy-1-trifluoromethyl-2,2,2-trifluoroethyl)aniline	40	Ether	80	N-(1-Hydroxy-1-trifluoromethyl-2,2,2-trifluoroethyl)-aniline—N,N-dimethylaniline, 1:1	31
(VI)	1-Amino-2-(1-hydroxy-1-trifluoromethyl-2,2,2-trifluoroethyl)naphthalene	1	$CHCl_3$	20	1-Naphthylamine (I), 1:1	86
(VII)	1-Amino-2,4-bis(1-hydroxy-1-trifluoromethyl-2,2,2-trifluoroethyl)naphthalene	1	$CHCl_3$	20	(VI)—(I), 1:2	71
(VIII)	1-Amino-2-(1-hydroxy-1-trifluoromethyl-2,2,2-trifluoroethyl)-4-(1-hydroxy-1-methoxycarbonyl-2,2,2-trifluoroethyl) naphthalene	6	CCl_4	80	(VI)—(II), 1:1	88
(IX)	6-(1-Hydroxy-1-trifluoromethyl-2,2,2-trifluoroethyl)-3-methylaniline	24	CCl_4	20	3-Methylaniline—(I), 1:1	89
(X)	3-Hydroxy-2-oxo-3-trifluoromethyl-6-methylindoline	24	CCl_4	20	3-Methylaniline—(II), 1:1	76
(XI)	4-(1-Hydroxy-1-trifluoromethyl-2,2,2-trifluoroethyl)-2-methylaniline	240	Freon-113	20	2-Methylaniline—(I), 1:1	79
(XII)	4-(1-Hydroxy-1-methoxycarbonyl-2,2,2-trifluoroethyl)-2-methylaniline	240	Freon-113	20	2-Methylaniline—(II), 1:1	71
(XIII)	3-Hydroxy-2-oxo-3-trifluoromethyl-7-methylindoline	6	C_6H_6	120	2-Methylaniline—(II), 1:2	89
(XIV)	4-(1-Hydroxy-1-trifluoromethyl-2,2,2-trifluoroethyl)-2,6-dimethylaniline	24	Freon-113	20	2,6-Dimethylaniline—(I), 1:1	94
(XV)	4-(1-Hydroxy-1-methoxycarbonyl-2,2,2-trifluoroethyl)-2,6-dimethylaniline	24	Freon-113	20	2,6-Dimethylaniline—(II), 1:1	88
(XVI)	4-(1-Hydroxy-1-trifluoromethyl-2,2,2-trifluoroethyl)-2,5-dimethoxyaniline	24	$CHCl_3$	20	2,5-Dimethoxyaniline—(I), 1:1	91
(XVII)	4(1-Hydroxy-1-methoxycarbonyl-2,2,2-trifluoroethyl)-2,5-dimethoxyaniline	24	$CHCl_3$	20	2,5-Dimethoxyaniline—(II), 1:1	84
(XVIII)	2-[N-(2,4,6-Trimethylphenyl)imino]trifluoropropanoic acid methyl ester	8	Toluene	100	Mesidine—(II), 1:1	93
(XIX)	2-(N-Phenylimino)trifluoropropanoic acid methyl ester	8	Toluene	100	Aniline—(II), 1:1	35
(XX)	4-(1-Hydroxy-1-trifluoromethyl-2,2,2-trifluoroethyl)-2-chloroaniline	60	$MeNO_2$	65	2-Chloroaniline—(I), 1:1	85

TABLE 2. Properties of Compounds (IV)-(XX)*

Compound	R_f	Mp, °C	Found/Calculated, %			Empirical formula
			C	H	N	
(IV)	0,23	152–154 (pentane)	41.53 / 41,69	2,40 / 2,70	5,19 / 5,40	$C_9H_7F_6NO$
(V)	0,75	80–81 (pentane)	45.71 / 45,99	3,58 / 3,83	4,60 / 4,87	$C_{11}H_{11}F_6NO$
(VI)	0,49	164–166 $CHCl_3$	50.21 / 50,49	3.12 / 2,91	4,44 / 4,59	$C_{13}H_9F_6NO$
(VII)	0,23	242–244 $CHCl_3$	40,01 / 40,42	2,08 / 1,89	3,15 / 2,95	$C_{16}H_9F_{12}NO_2$
(VIII)	0,2	151–153 CCl_4	43.56 / 43,87	2,64 / 2,58	2,91 / 3,01	$C_{17}H_{12}F_9NO_4$
(IX)	0,5	102–105 CCl_4	43,68 / 43,95	3,01 / 3,29	5,31 / 5,12	$C_{10}H_9F_6NO$
(X)	0,3	205–207 CCl_4	51,62 / 51,94	3,88 / 3,46	6,22 / 6,06	$C_{10}H_8F_3NO_2$
(XI)	0,45	135–136 Freon-113	47.42 / 47,61	3,11 / 3,29	5,01 / 5,12	$C_{10}H_9F_6NO$
(XII)	0,51	112–114 Freon-113	49.88 / 50,19	4.18 / 4,56	5,70 / 5,32	$C_{11}H_{12}F_3NO_3$
(XIII)	0,4	125–127 C_6H_6	51.71 / 51,94	3,14 / 3,46	6,24 / 6,06	$C_{10}H_8F_3NO_2$
(XIV)	0,5	173–175 Freon-113	46.12 / 45,99	4.12 / 3,83	5,03 / 4,87	$C_{11}H_{11}F_6NO$
(XV)	0,65	160–162 Freon-113	51,63 / 51,98	4,85 / 5,05	5,11 / 5,05	$C_{12}H_{14}F_3NO_3$
(XVI)	0,55	142–145 $CHCl_3$	41,19 / 41,38	3.57 / 3,44	3,99 / 4,38	$C_{11}H_{11}F_6NO_3$
(XVII)	0,32	100–102 $CHCl_3$	46,41 / 46,60	4,31 / 4,53	4,59 / 4,53	$C_{12}H_{14}F_3NO_5$
(XVIII)	0,98	–	56,84 / 57,14	5,22 / 5,13	5,16 / 5,13	$C_{13}H_{14}F_3NO_2$ †
(XIX)	0,93	–	51.81 / 51,95	3,38 / 3,46	6,11 / 6,06	$C_{10}H_8F_3NO_2$ †
(XX)	0,6	120–122 $MeNO_2$	36.71 / 36,80	2,30 / 2,04	4,57 / 4,77	$C_9ClH_6F_6NO$

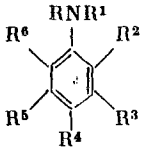
*Compound (IV) was described earlier [1]; (VI), (IX), (XI), (XVI), (XX) [4].
†In CCl_4–methyl ethyl ketone, 3:1.

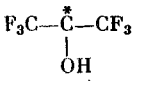


C-Alkylation products are formed much more readily by some ring-substituted anilines and condensed arylamines (see Table 1). For example, α-naphthylamine, in contrast to the data in [4], reacts quantitatively with compound (I) to form the C^2-adduct (VI) after 1 h at 20°C. Under the same conditions at an excess of (I), α-naphthylamine is converted to the 2,4-dialkylation product (VII), and compound (VI) reacts with ketoester (II) at a moderate temperature to give compound (VIII).

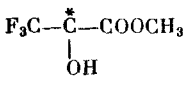
Among the toluidines m-toluidine reacts especially readily (20°C, 24 h) with compounds (I) and (II). C-Hydroxyalkylation takes place exclusively at the o-position with respect to the NH_2 group, affording adduct (IX) and indoline (X). o-Toluidine reacts more slowly, affording C^4-hydroxyalkylation products (XI) and (XII). However, under drastic conditions o-toluidine undergoes o-substitution by ketoester (II) to give indoline (XIII), which apparently results from N-acylation followed by C-alkylation. p-Toluidine and p-anisidine do not form C-hydroxyalkylation products even at 80°C.

TABLE 3. ^{13}C NMR Spectral Parameters of Compounds (IV), (V), (VII)-(XII), and (XX)†





(A)

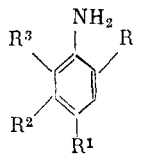


(B)

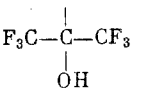
Compound	Substituent	δ, ppm (acetone)											
		C¹	C²	C³	C⁴	C⁵	C⁶	R = A or B				R ≠ A; B	¹⁹F
								CF_3 ($^1J_{C-F}$, Hz)	* C	C=O	OCH_3		
(IV)	R=R¹=R²=R³=R⁵=R⁶=H; R⁴=A	150,5	114,8	128,6	120,7	128,6	114,8	124,4 (286,2)	78,1	–	–	–	–
(V)	R²=R³=R⁵=R⁶=H R=R¹=CH_3; R⁴=A	152,3	112,4	128,4	118,3	128,3	112,4	124,3 (286)	78,1	–	–	40	–
(VII)	R=R¹=R³=H R⁵=R⁶=–(CH=CH)₂– R²=R⁴=A	146,5	102,2	125,5	124,8	132,1	112,2	124,6 (286,4) 125,1 (288,2)	79,4 80,0			121,2 124,0 125,8 126,8	–5,12 –4,09 (1 : 1)
(VIII)	R=R¹=R³=H R⁵=R⁶=–(CH=CH)₂– R²=A, R⁴=Б	145,5	103,5	124,1	123,7	131,0	117,6	124,1 (285,6) 124,3 (285,6)	79,3 79,3	166,5	51,7	121,5 124,0 125,5 126,5	–4,32 –3,65 (2 : 1)
(IX)	R=R¹=R²=R⁴=R⁵=H R³=CH_3; R⁶=A	142,7	118,9	124,5	116,3	125,2	106,0	75,9	121,8			15,6	
(XI)	R=R¹=R²=R⁵=R⁶=H R²=CH_3; R⁴=A	146,5	119,9	127,3	125,1	124,1	112,5	75,9	121,5			15,6	
(XII)	R=R¹=R³=R⁵=R⁶=H R²=CH_3; R⁴=Б	145,8	120,0	127,0	127,3	123,0	112,6	76,9	121,2	167,7	51,4	15,6	
(XX)	R=R¹=R³=R⁵=R⁶=H R²=Cl; R⁴=A	144,0	118,0	126,6	124,9	125,0	113,8	76,5	122,2				

†The signals were assigned on the basis of the data in [6]. ^{13}C NMR spectrum of compound (X) (δ, ppm, acetone): 20.3 (CH_3), 76.2 (C^3), 110.9 (C^7), 124.4 (CF_3), $^1J_{C-F}$ = 284.6 Hz, 124.8 (C^5), 126.8 (C^{3a}), 127.4 (C^6), 132.0 (C^4), 143.1 (C^{7a}), 172.0 (C^2). ^{19}F NMR spectrum (δ, ppm, acetone): 1.29.

TABLE 4. ^1H and ^{19}F NMR Spectra of Compounds (XIII)-(XVII)*



(A)

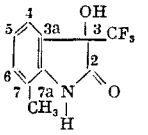


(B)

Compound	Substituent R	δ, ppm (acetone-d_6)						
		H^3	H^4	H^5	H^6	OCH_3	CH_3	^{19}F
(XIV)	R^2=H, R=R^3=CH_3 R^1= A	7,05 s		7,05 s			2,05s	−3,2 s
(XV)	R^2=H, R=R^3=CH_3 R^1= B	7,03 s		7,03 s		3,8s	2,05 s	−3.09s
(XVI)	R^3=H, R=R^2=OCH_3 R^1= A	6,9 s			6,6 s	3,9s 3,7 s		
(XVII)	R^3=H, R=R^2=OCH_3 R^1= B	7.01s			6,32 s	3,6 s 3,65 s 3,7 s		

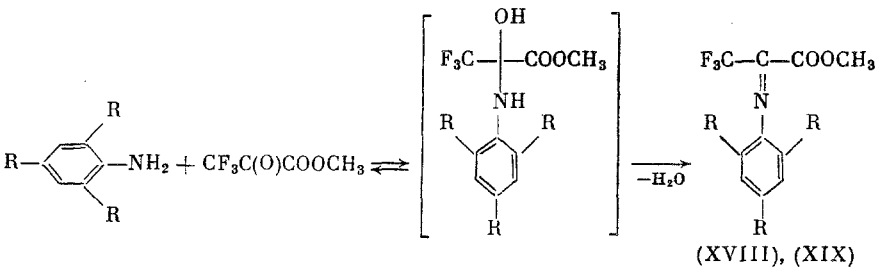
*PMR spectrum of (XIII) (δ, ppm, acetone-d_6): 2.3 s (CH_3), 7.0 d. d (H^5), 7.3 d, 7.4 d (H^6, H^4). ^{19}F NMR spectrum (δ, ppm, acetone): 1.3 s.

The presence of two donor substituents in the phenyl ring increases the susceptibility of aniline toward C-hydroxyalkylation. Thus, in the presence of compounds (I) and (II), 2,6-xylidine and 2,5-dimethoxyaniline are converted almost quantitatively to C^4-hydroxyalkylation products (XIV)-(XVII) after one day at 20°C. On the other hand, mesidine under mild conditions is inert toward polyfluorocarbonyl compounds; it does not form stable geminal aminohydroxy compounds due to steric hindrance. When heated together with compound (I), mesidine affords resin-forming products; with compound (II) in toluene, after azeotropic distillation of water, it is converted to anil (XVIII).† Under these conditions aniline reacts with (II)



(XIII)

to form anil (XIX) in a yield of 30%. This indicates that N-hydroxyalkylation products of arylamines with ketoester (II) are stabilized by elimination of water.



R = CH_3 (XVIII); R = H (XIX)

N-(α-Hydroxyhexafluoroisopropyl)anilines do not posses similar properties [1].

The data presented above are summarized in Table 1, which shows that differences in the reactivity of arylamines may be explained solely on the basis of steric effects of the phenyl ring substituents. The presence of o-substituents increases the susceptibility of the aryl-

†For previous communication, see [10].

amine toward C-hydroxyalkylation. Thus, even o-chloroaniline reacts with ketone (I) under relatively mild conditions (60°C), affording the C^4-hydroxyalkylation product (XX) in a high yield. In addition, the ease of C^2-hydroxyalkylation of m-toluidine by ketone (I) indicates that increasing the ring C-nucleophilicity is another way of overcoming the inhibitory effects of equilibrium N-hydroxyalkylation.

The physical characteristics and composition of the synthesized compounds are summarized in Table 2. The ^{13}C, ^{1}H, and ^{19}F NMR spectra are shown in Tables 3 and 4. The spectral characteristics of anils (XVIII) and (XIX) are presented in the experimental section.

EXPERIMENTAL

^{1}H, ^{19}F, and ^{13}C NMR spectra were obtained at 20°C on a Bruker WR-200SY spectrometer at operating frequencies of 200.12, 188.31, and 50.31 MHz, respectively. Chemical shifts were determined relative to TMS (^{1}H, ^{13}C) and CF_3COOH (internal standard, ^{19}F). R_f values are presented for Silufol UV-254 plates in CCl_4–acetone (3:1). UV spectra were recorded on a Specord M-40 apparatus in pentane. IR spectra were recorded on a Specord M-80 apparatus in petrolatum oil. Compounds (IV)-(XVII) and (XX) were obtained in a covered vessel under the conditions shown in Table 1 and were purified by crystallization.

2-[N-(2,4,6-Trimethylphenyl)imino]trifluoropropanoic Acid Methyl Ester (XVIII). A solution of 6.75 g mesidine in 50 ml anhydrous toluene and 8.0 g of compound (II) were boiled for 8 h, with azeotropic distillation of water. After removal of the solvent, the residue was distilled in a vacuum. A 12.7-g yield of a reddish liquid was obtained; bp 93°C (4 mm), n_D^{20} 1.4600. UV spectrum (λ_{max}, nm): 259.6 (ε 912); 358.2 (ε 262). IR spectrum (ν, cm^{-1}): 1040 (C–O); 1689 (C=N); 1750 (C=O). ^{13}C NMR spectrum (δ, ppm, in CCl_4 relative to TMS): 15.33 s (2,6-CH_3), 18.65 s (4-CH_3), 50.39 s (OCH_3), 116.06 q (CF_3, $^{1}J_{C-F}$ = 278.7 Hz), 122.24 s (C^2, C^6), 126.60 s (C^3, C^5), 132.00 s (C^4), 140.78 s (C^1), 148.56 q (C=N, $^{2}J_{C-F}$ = 31.9 Hz), 157.01 s (C=O).

2-(N-Phenylimino)trifluoropropanoic Acid Methyl Ester (XIX). A solution of 9.3 g aniline in 50 ml anhydrous toluene and 26.0 g of compound (II) were boiled for 8 h, with azeotropic distillation of water. The mixture was cooled, the precipitate was filtered, and the solvent of the mother liquor was removed in a vacuum. The residue was loaded on a column with 250 g silica gel and was eluted first with CCl_4 (2 liters), then with CCl_4–acetone (10:1). An 8-g yield of a yellow liquid was obtained; bp 85°C (7 mm), n_D^{20} = 1.4600. UV spectrum (λ_{max}, nm): 214.4 (ε 3820); 323.2 (ε 1455). IR spectrum (ν, cm^{-1}): 1043 (C–O), 1685 (C=N), 17.52 (C=O). ^{13}C NMR spectrum (δ, ppm, in CCl_4 relative to TMS): 50.50 s (OCH_3), 116.42 q (CF_3, $^{1}J_{C-F}$ = 277.2 Hz), 117.47 s (C^2, C^4), 125.27 s (C^4), 127.20 s (C^3, C^5), 144.70 s (C^1), 146.84 q (C=N, $^{2}J_{C-F}$ = 32.8 Hz); 157.74 s (C=O).

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