Reactions of polyfluorocarbonyl compounds and their trifluoroacetylimines with fused heterocycles

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C-Hydroxy- and *C*-aminoalkylation of iminodibenzyl, iminostilbene, phenoxazine, and phenothiazine with hexafluoroacetone, methyl trifluoropyruvate, and their trifluoroacetylimines were investigated. The substitution occurred at one or several *para*- and *ortho*-positions to the N atom of the heterocycles. In the case of methyl trifluoropyruvate and its derivative the substitution in the *ortho*-position was accompanied by the formation of lactams.

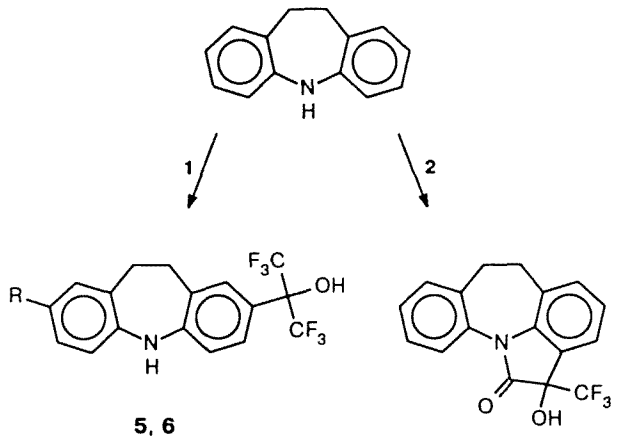
Key words: iminodibenzyl, iminostilbene, phenoxazine, phenothiazine; hexafluoroacetone, methyl trifluoropyruvate, imines; *C*-hydroxyalkylation, *C*-aminoalkylation.

The reaction of diphenylamine with an equimolar amount of hexafluoroacetone (**1**) affords a complex mixture of compounds from which a product of 2-hydroxyalkylation can be isolated in a low yield.[1] However, boiling of diphenylamine with an excess of hexafluoroacetone hydrate gives a product of 4,4′-dihydroxyalkylation of arylamine.[2] 2-Hydroxyalkylation of diphenylamine with methyl trifluoropyruvate (**2**) is accompanied by the formation of lactams.[3] The reaction of diphenylamine with highly electrophilic methyl trifluoropyruvimines, in particular with trifluoroacetylimine (**3**), proceeds similarly. In this case, however, the reaction is complicated by the competitive formation of aminals that results in a decrease in the yield of products.[4] Unlike the corresponding trifluoropyruvic acid derivative **3**, hexafluoroacetone trifluoroacetylimine (**4**) undergoes heterocyclization with diphenylamine with the participation of the carbonyl group of the trifluoroacetyl moiety to afford 1-phenyl-2,2,4-tris(trifluoromethyl)-1,4-dihydroquinazoline.[5]

This work studied the reactions of fused heterocycles, which were synthesized from diphenylamine and its derivatives, with hexafluoroacetone, methyl trifluoropyruvate, and their trifluoroacetylimines **3** and **4**.

The reaction of equimolar amounts of iminodibenzyl and ketone **1** in CCl_4 at 20 °C affords a mixture of 2-hydroxy- (**5**) and 2,8-dihydroxyalkylation (**6**) products; the yield of compound **5** (Scheme 1) is 40 %. Product **6** is solely formed in the case of a twofold excess of hexafluoroacetone; it was also obtained by refluxing of iminodibenzyl in an excess of hexafluoroacetone hydrate. The attempts to introduce the third hexafluoropropanolic group result only in resinification of the reaction mixture.

Scheme 1



5, 6

5: R = H
6: R = $C(CF_3)_2OH$

7

Similar to diphenylamine, iminodibenzyl reacts with ketoester **2** to form lactam **7**.

Iminostilbene is less active in the reactions with ketone **1** and ketoester **2**. The reaction of equimolar amounts of iminostilbene and compound **1** in CCl_4 (15 days at 20 °C) affords 2-hydroxyalkylation product **8** in a quantitative yield (Scheme 2). The disubstituted product is not formed even with a twofold excess of hexafluoroacetone.

Iminostilbene does not react with ketoester **2** even upon prolonged heating at 100 °C.

As could be expected, phenoxazine is far more active in reactions with polyfluorocarbonyl compounds. For ex-

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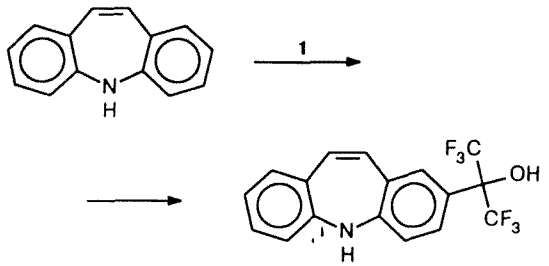
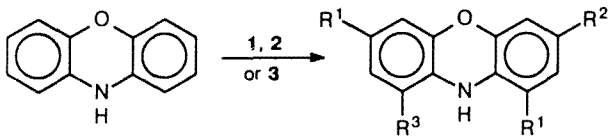
Scheme 2



8

ample, its reaction with an excess of ketone **1** (1 : 6) in $MeNO_2$ at 20 °C results in the formation of mainly *C,C,C*-trihydroxyalkylation product **9**, which was isolated in a 65 % yield (Scheme 3). The same reaction in $CHCl_3$ gives a mixture of tri- and tetrasubstituted phenazines (**9** and **10**, respectively) in a ~1 : 1 ratio (according to their ^{19}F NMR spectra) in a ~80 % total yield. Compound **10** was isolated in an individual form by fractional crystallization.

Scheme 3



9—12

9: $R^1 = R^2 = C(CF_3)_2OH$, $R^3 = H$

10: $R^1 = R^2 = R^3 = C(CF_3)_2OH$

11: $R^1 = R^3 = H$, $R^2 = C(CF_3)(COOMe)OH$

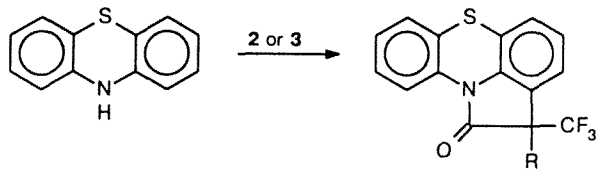
12: $R^1 = R^3 = H$, $R^2 = C(CF_3)(COOMe)NHC(O)CF_3$

The reaction of equimolar amounts of phenoxazine and hexafluoroacetone in $CHCl_3$ affords a complex mixture of products; so does the similar reaction with polyfluoroacetylimine **4**.

Unlike compound **1**, methyl trifluoropyruvate *C*-hydroxyalkylates regioselectively phenoxazine. The 2-hydroxyalkylation product **11**, which was isolated in a 71 % yield, is solely formed at an equimolar ratio of the reagents. Similarly to ketoester **2**, its trifluoroacetylimine **3** reacts with phenoxazine; the reaction proceeds at 20 °C in $CHCl_3$ affording compound **12** (see Scheme 3).

Unlike phenoxazine, phenothiazine reacts with ketoester **2** to form lactam **13** (Scheme 4). The latter is obtained in a high yield if the reaction is carried out in $CHCl_3$ and in the presence of a twofold excess of ketoester for binding the forming methanol. Lactam **14** is formed upon boiling of phenothiazine with imine **3** in $CHCl_3$.

Scheme 4



13, 14

13: R = OH

14: $R = NHC(O)CF_3$

Reactions of phenothiazine with ketone **1** and its trifluoroacetylimine **4** afford complex mixtures of products.

The structure of compounds obtained was established by ^1H, ^{13}C, and ^{19}F NMR spectral data and elemental analysis. The main physicochemical constants of compounds **5—14** are given in Table 1.

ESR spectroscopy revealed the appearance of radicals upon mixing of phenoxazine and phenothiazine with ketoester **2** in $CHCl_3$. Further investigation of the role of radicals in *C*-hydroxylation processes is of interest.

Experimental

^{13}C NMR spectra were recorded on a Bruker-200 SY spectrometer (50.31 MHz) at 20 °C in acetone-d_6. ^1H and ^{19}F NMR spectra were obtained on a Bruker-AC-200F instrument (200.00 and 188.31 MHz, respectively) in acetone-d_6. $SiMe_4$ was used as the internal standard (for ^1H and ^{13}C NMR) and CF_3COOH as the external standard (for ^{19}F NMR). R_f values for compounds **5—8** were determined on Silufol UV_{254} plates (Kavalier) in a CCl_4—acetone mixture.

2-(2-Hydroxy-1,1,1,3,3,3-hexafluoroprop-2-yl)iminodibenzyl (5). Ketone **1** (1.88 g, 11 mmol) was condensed to a solution of iminodibenzyl (1.95 g, 10 mmol) in CCl_4 (20 mL) in a closed flask. The flask was kept at 20 °C for 18 h, then the solvent was evaporated, and the residue was crystallized from hexane to afford 1.43 g of compound **5**. ^1H NMR, δ: 3.05 (br.s, 4 H, H(10), H(11)); 7.70 (m, 2 H, H(4), H(6)); 7.0 (m, 3 H, H(1), H(3), H(9)); 7.40 (m, 2 H, H(7), H(8)); 8.80 (br.s, 1 H, OH). ^{19}F NMR, δ: −3.00 (s).

2,8-Di(2-hydroxy-1,1,1,3,3,3-hexafluoroprop-2-yl)iminodibenzyl (6). Ketone **1** (3.32 g, 20 mmol) was condensed to a solution of iminodibenzyl (1.95 g, 10 mmol) in CCl_4 (20 mL) in a closed flask. The flask was kept at 20 °C for 18 h, then the solvent was evaporated, and the residue was poured into 1 L of water. The precipitate was filtered off to afford 3.39 g of compound **6**. ^1H NMR, δ: 3.15 (s, 4 H, H(10), H(11)); 7.10 (d, 2 H, H(3), H(7)); 7.25 (s, 2 H, H(1), H(9)); 7.42 (br.d, 2 H, H(4), H(6)); 8.80 (br.s, 2 H, OH).

Dibenzo[*b,f*]azepino[4,12-*b,c*]-2-hydroxy-1-oxo-2-trifluoromethyl-6,7-dihydropyrroline (7). Ketoester **2** (2.0 g, 12 mmol) was added to a solution of iminodibenzyl (1.95 g, 10 mmol) in

Table 1. Characteristics of compounds **5—14**

Compound	Yield (%)	M.p./ °C (solvent)	R_f (CCl_4 : Me_2CO)	Found / Calculated (%)			Molecular formula
				C	H	N	
5	64.0	131—132 (hexane)	0.24 (6 : 1)	56.50 / 56.71	3.60 / 3.58	3.87 / 3.49	$C_{17}H_{13}F_6NO$
6	39.0	155—156	0.65 (6 : 1)	45.54 / 45.59	2.46 / 2.39	2.65 / 2.78	$C_{20}H_{13}F_{12}NO_2$
7	90.0.'	183—184 (CCl_4)	0.6 (6 : 1)	63.95 / 63.81	3.76 / 3.88	4.38 / 4.49	$C_{17}H_{12}F_3NO_2$
8	89.0	200—201 ($CHCl_3$)	0.24 (6 : 1)	56.82 / 56.91	3.06 / 3.21	3.89 / 3.71	$C_{17}H_{11}F_6NO$
9	65.0	153—154 (CCl_4)	0.50 (3 : 1)	36.85 / 37.00	1.41 / 1.32	1.79 / 2.06	$C_{21}H_9F_{18}NO_4$
10	38.0*	151—152 (CCl_4)	0.33 (3 : 1)	34.23 / 34.00	0.98 / 1.06	1.81 / 1.65	$C_{24}H_9F_{24}NO_5$
11	71.0	84—86 (pentane)	0.63 (3 : 1)	56.63 / 57.12	3.54 / 3.81	4.13 / 3.39	$C_{16}H_{12}F_3NO_4$
12	34.5	161—164 (CCl_4)	0.65 (3 : 1)	49.32 / 49.77	3.01 / 2.76	6.28 / 6.45	$C_{18}H_{12}F_6N_2O_4$
13	86.2	195—196 (hexane—$CHCl_3$)	0.62 (10 : 1)	55.48 / 55.73	2.46 / 2.48	4.35 / 4.33	$C_{15}H_8F_3NO_2S$
14	15.5	176—177 (hexane—$CHCl_3$)	0.57 (10 : 1)	48.74 / 48.80	1.93 / 1.91	6.52 / 6.70	$C_{17}H_8F_6N_2O_2S$

*The content of **10** (%) in the final reaction products (according to the ^{19}F NMR spectra) is given.

$CHCl_3$ (30 mL) in a closed flask. The flask was kept at 20 °C for 18 h. The precipitate was filtered off and washed with CCl_4 (50 mL) to afford 2.9 g of compound **7**. ^1H NMR, δ: 3.02 (br.s, 4 H, H(6), H(7)); 7.16 (dd, 1 H, H(4)); 7.32 (m, 4 H, H(8), H(9), H(10), H(11)); 7.50 (d, 1 H, (H(5)); 7.75 (d, 1 H, H(3)). ^{19}F NMR, δ: −1.0 (s).

2-(2-Hydroxy-1,1,1,3,3,3-hexafluoroprop-2-yl)iminostilbene (8). Ketone **1** (1.7 g, 11 mmol) was condensed to a solution of iminostilbene (1.93 g, 10 mmol) in CCl_4 (20 mL) in a closed flask. The flask was kept at 20 °C for 15 days. Then the flask was opened, the solvent was evaporated, and the residue was crystallized from $CHCl_3$ to afford 2.51 g of compound **8**. ^1H NMR, δ: 6.20 (br.s, 2 H, H(10), H(11)); 6.62 (d, 1 H, H(4)); 6.70—6.83 (m, 3 H, H(6), H(8), H(9)); 7.00 (dd, 1 H, H(7)); 7.15 (s, 1 H, H(1)); 7.38 (d, 1 H, H(3)). ^{19}F NMR, δ: −2.9 (s, CF_3).

2,4,8-Tri(2-hydroxy-1,1,1,3,3,3-hexafluoroprop-2-yl)phenoxazine (9). Ketone **1** (5 g, 30 mmol) was condensed to a solution of phenoxazine (0.91 g, 5 mmol) in $MeNO_2$ (6 mL) in a glass tube at −78 °C. The tube was sealed and kept at 20 °C for 6 days. Then the tube was cooled to −78 °C, opened, and warmed to 20 °C. The solvent was removed, and the residue was crystallized from CCl_4 to afford 2.2 g of commpound **9** as white crystals. ^1H NMR, δ: 6.80 (d, 1 H, H(6), $J_{H(6),H(7)}$ = 8.1 Hz); 6.83 (s, 1 H, H(9)); 7.00 (d, 1 H, H(7), $J_{H(7),H(6)}$ = 8.1 Hz); 7.05 (s, 1 H, H(1)); 7.45 (s, 1 H, H(3)); 7.65 (s, 1 H, OH); 8.35 (s, 1 H, OH); 8.45 (s, 1 H, OH); 10.0 (s, 1 H, NH). ^{19}F NMR, δ: −3.97 (s, CF_3); −3.81 (s, CF_3); −2.80 (s, CF_3).

2,4,6,8-Tetra(2-hydroxy-1,1,1,3,3,3-hexafluoroprop-2-yl)phenoxazine (10). Ketone **1** (5 g, 30 mmol) was condensed to a solution of phenoxazine (0.91 g, 5 mmol) in $CHCl_3$ (6 mL) in a glass tube at −78 °C. The tube was sealed and kept at 20 °C for 6 days. Then the tube was cooled to −78 °C, opened, and warmed to 20 °C. The precipitate was filtered off and washed with pentane to afford 2.6 g of a mixture of compounds **9** and **10** that were isolated in an individual form by fractional crystallization from CCl_4.

Compound **10**. ^1H NMR, δ: 7.10 (s, 2 H, H(1), H(9)); 7.40 (s, 2 H, H(3), H(7)); 7.70 (s, 2 H, 2 OH); 8.45 (s, 2 H, 2 OH); 10.15 (s, 1 H, NH). ^{19}F NMR, δ: −3.80 (s, CF_3); 2.79 (s, CF_3).

2-(2-Hydroxy-1,1,1,3,3,3-hexafluoroprop-2-yl)phenoxazine (11). Ketoester **2** (0.8 g, 5.1 mmol) was added to a solution of phenoxazine (0.91 g, 5 mmol) in $CHCl_3$ (6 mL) with stirring. The mixture was kept at 20 °C for ~12 h. The solvent was removed, and the residue was crystallized from pentane to afford 1.2 g of compound **11**. ^1H NMR, δ: 3.75 (s, 3 H, MeO); 6.75 (m, 8 H, H(1), H(3), H(4), H(6)—H(9)); 7.10 (s, 1 H, OH); 7.47 (s, 1 H, NH). ^{13}C NMR, δ: 54.26 (OMe); 81.89 (C—CF_3, $^2J_{C,F}$ = 28.3 Hz); 117.02 (C(2)); 115.08 (C(1), C(3)—C(9)); 116.10, 117.60, 121.09, 122.57, 123.69, 125.01, 125.05 (CF_3, $J_{C,F}$ = 286.00 Hz); 132.41 (C(4a), C(6a)); 134.46, 144.19 (C(1a), C(9a)); 145.88, 168.00 (COO).

2-(1-Trifluoroacetylamino-1-methoxycarbonyl-2,2,2-trifluoroethyl)phenoxazine (12). Imine **3** (0.261 g) was added to a solution of phenoxazine (0.183 g, 1 mmol) in $CHCl_3$ (1 mL) with stirring. The mixture was kept for 21 days. The precipitate was filtered off and crystallized from CCl_4 to afford 0.15 g of compound **12** as white crystals. ^{13}C NMR, δ: 54.11 (MeO); 67.71 (C—CF_3, $^2J_{C,F}$ = 27.1 Hz); 116.71 (CF_3—CO, $J_{C,F}$ = 278.5 Hz); 124.90 (CF_3—C≡, $J_{C,F}$ = 286.0 Hz); 114.50 (C(2)); 114.10, 115.00, 115.45, 116.53, 122.51, 124.20, 125.40 (C(1), C(3)—C(9)); 133.00, 136.05 (C(4a), C(6a)); 144.85, 145.00 (C(1a), C(9a)); 157.50 (CO); 166.11 (COO).

2-Hydroxy-1-oxo-2-trifluoromethyl-1a-aza-6-thia-1a,6-dihydroaceanthrene (13). Ester **2** (3.3 g, 21 mmol) was added to a solution of phenothiazine (2.0 g, 10 mmol) in $CHCl_3$ (20 mL) with stirring. The mixture was kept at 20 °C for 4 days. The precipitate was filtered off and crystallized from a hexane—

$CHCl_3$ mixture (3 : 1) to afford 2.8 g of compound **13**. ^1H NMR, δ: 7.40—7.00 (m, 7 H); 8.62 (m, 1 H). ^{19}F NMR, δ: 1.01 (s, CF_3). ^{13}C NMR, δ: 76.45 (q, C (2), $^2J_{C,F}$ = 30 Hz); 124.26 (q, CF_3, $J_{C,F}$ = 283 Hz); 116.51, 119.25, 120.19, 123.52, 124.63, 127.43, 127.68, 127.87, 128.17, 128.52, 133.34, 137.49 (C(2b), C(2a), C(3), C(4), C(5), C(5a), C(7), C(7a), C(8), C(9), C(10), C(10a)); 169.55 (C(1), C=O).

1-Oxo-2-trifluoroacetylamino-2-trifluoromethyl-1a-aza-6-thia-1a,6-dihydroaceanthrene (14). Imine **3** (5.1 g, 21 mmol) was added to a solution of phenothiazine (2.0 g, 10 mmol) in $CHCl_3$ (20 mL) with stirring. The mixture was refluxed for 30 h, the solvent was removed *in vacuo*, and the residue was crystallized from a hexane—$CHCl_3$ mixture (3 : 1) to afford 0.65 g of compound **14**. ^1H NMR, δ: 7.10—7.30 (m, 7 H); 8.65 (m, 1 H). ^{19}F NMR, δ: −3.4 (s, CF_3); −3.1 (s, CF_3). ^{13}C NMR, δ: 69.20 (q, C(2), $J_{C,F}$ = 30 Hz); 120.11 (q, CF_3, $J_{C,F}$ = 284 Hz); 127.09 (q, CF_3, $J_{C,F}$ = 281 Hz); 120.85, 123.25, 124.23, 124.60, 127.40, 131.55, 131.93, 132.00, 132.45, 132.65, 137.35, 142.20 (C(2b), C(2a), C(3), C(4), C(5), C(5a), C(7), C(7a), C(8), C(9), C(10), C(10a)); 161.50 (—NHC=O); 169.95 (C(1), C=O).

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References

1. V. D. Sviridov, N. D. Chkanikov, A. F. Kolomiets, and A. V. Fokin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1991, 952 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1991, **40**, 847 (Engl. Transl.)].
2. E. E. Gilbert, US Pat. 3532753; *Chem. Abstrs.*, 1970, **73**, No. 23, 120296e.
3. A. E. Zelenin, N. D. Chkanikov, A. F. Kolomiets, and A. V. Fokin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1986, 2080 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1986, **35**, 1895 (Engl. Transl.)].
4. S. N. Osipov, N. D. Chkanikov, A. F. Kolomiets, and A. V. Fokin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 1648 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, **38**, 1512 (Engl. Transl.)].
5. N. D. Chkanikov, V. L. Vershinin, M. V. Galakhov, A. F. Kolomiets, and A. V. Fokin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1989, 126 [*Bull. Acad. Sci. USSR, Div. Chem. Sci.*, 1989, **38**, 113 (Engl. Transl.)].

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