TRIFLUOROACETYLATION OF 3-HALO-9-METHYLCARBAZOLES

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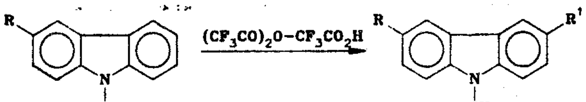
Trifluoroacetylation of 3-halo-9-methylcarbazoles at 110°C proceeds at 6-position. In the case of 3-bromo- and 3-iodo-derivatives, the reaction is complicated by competing processes of dehalogenation, followed by the halogenation of the substrate, leading to 3,6-dihalo derivatives.

The development of methods for introducing fluorine-containing fragments into organic molecules is one of the important problems of fine organic synthesis [1]. We have already shown [2] that 9-methylcarbazole (Ia) is readily trifluoroacetylated, but the reaction is accompanied by considerable resin formation that decreases the yields of the required end products. In the present work, we studied the influence of electron acceptor substituents in the ring of carbazole Ia on the course of the trifluoroacetylation reaction.



Ia-d IIa-f

I—II a R=H, b R=Cl, c R=Br, d R=I; II a-d R'=$COCF_3$, d R=R'=Br, e R=R'=I

It was found that in contrast to carbazole Ia, compounds Ib, c, IIa, and 9-methyl-3-nitrocarbazole do not react at 20°C with $(CF_3CO)_2O$ and its mixtures with CF_3CO_2H in dichloroethane (DCE). The two last derivatives of carbazole are not acetylated, even at 110°C.

The chloro derivative Ib becomes smoothly acetylated by a $(CF_3CO)_2O:CF_3CO_2H$ (1:1) mixture at 110°C, to form 9-methyl-3-trifluoroacetyl-6-chlorocarbazole (IIb) in a yield of 63% and an inappreciable amount of a resin. By using TLC and mass spectrometry, carbazole Ib and 1,1-bis(9-methyl-3-chloro-6-carbazolyl)-2,2,2-trifluoroethane (III) were also detected in the reaction mixture. We obtained a compound with a similar structure in the reaction of carbazole Ia with CF_3CO_2H [3]. At the same time, even traces of 1,1,1-tris-(9-methyl-3-chloro-6-carbazolyl)-2,2,2-trifluoroethane (IV) were not detected, although its nonchlorinated analog is formed under these conditions [2] during trifluoroacetylation of carbazole Ia. The following compounds were chromatographically isolated from the reaction mixture obtained by trifluoroacetylation of the chloro derivative Ib under conditions of lower acidity of the medium [$(CF_3CO)_2O:CF_3CO_2H$, 10:1]: unreacted Ib (yield 41.5%), ketone IIb (22%), compound IV (8%), and 9-methyl-1-trifluoroacetyl-6-chlorocarbazole (V) (1.6%). Mass spectral analysis of a reaction mixture, obtained in the reaction of anhydrous $(CF_3CO)_2O$ with compound Ib, revealed only two components – the initial Ib and ketone IIb (Table 1). It is clear that neither higher nor too low acidity of the medium favor accumulation of compound IV in the reaction mixture. At 20°C, compound IV is readily formed from compounds Ib and IIb in the presence of CF_3CO_2H:

$$\mathrm{Ib} + \mathrm{IIb} \xrightarrow{CF_3CO_2H} \mathrm{IV},\ 33\%$$

These results show that the trifluoroacetylation of compounds Ia,b proceeds in similar directions.

The trifluoroacetylation of 3-iodo-9-methylcarbazole (Id) proceeds in a different way. In this case, the main reaction product is 3,6-diiodo-9-methylcarbazole (IIf) (yield 22%), together with the expected ketone IId (6.4%) and a considerable amount of a resin (25%). In addition, compounds Ia,d, IIa, and carbazole were recorded by mass spectrometry. Molecular

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TABLE 1. Composition of Reaction Mixtures during Trifluoroacetylation of Compounds Ib-d

Reaction product	m/z	I_{rel}, %*		Reaction product	m/z	I_{rel}, %*	Reaction product	m/z	I_{rel}, %*	
		1 : 3 : 3	1 : 3 —			1 : 3 : 3			2 : 5 : 1	1 : — : 6
Substrate Ib				Substrate Ic			Substrate Id			
I	215	37,2	24,5	Carbazole	167	0,6	Carbazole	167	1,0	0,6
	217	11,5	8,2	Ia	181	3,4	Ia	181	3,5	28,1
II	311	100,0	100,0	Ic	259	84,5	IIa	277	55,0	1,4
	313	33,3	33,3		261	67,6	Id	307	14,5	100,0
III	510	57,7	—	IIa	277	11,3	IId	403	8,0	—
	512	38,5	—	IIe	337	4,8	IIf	433	100,0	31,2
	514	12,8	—		339	10,4		360	—	39,2
					341	5,5		486	—	70,3
				IIc	355	92,9		612	—	4,6
					357	100,0				

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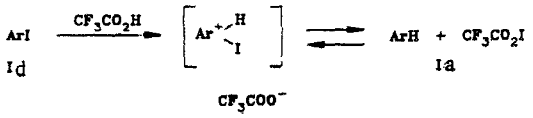
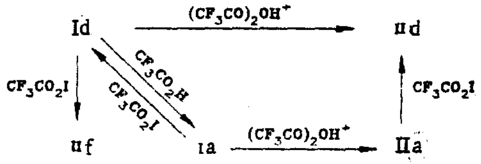
*Substrate — $(CF_3CO)_2O$:CF_3CO_2H system, molar ratio.

iodine was also detected. We explain the appearance of the diiodo derivative IIf by the formation of "positive iodine," probably in the form of trifluoroacetyl hypoiodite, a strong iodinating agent, in the course of the reaction [4]:



Here and below Ar = 9-methyl-3-carbazolyl

This is confirmed by the fact that CF_3CO_2H rapidly reacts with compound Id already at 20°C to form iodine, a resin and diiodo derivative IIf (yield 20%). The following scheme of the trifluoroacetylation of compound Id appears to be correct:



There is no path to compound IIa via the deiodination of ketone IId, since the latter is not changed by the action of CF_3CO_2H in dichloroethane at 110°C.

The formation of molecular iodine is clearly related to the occurrence of redox processes, for example

$$ArI + CF_3CO_2I \rightleftharpoons \left[ArI\right]^{+\cdot} + CF_3CO_2I^{-\cdot}$$

$$2\,CF_3CO_2I^{-\cdot} \longrightarrow 2\,CF_3CO_2^{-} + I_2$$

During the trifluoroacetylation of O-methyl-3-bromocarbazole (Ic) by an equimolar mixture $(CF_3CO)_2O$:CF_3CO_2H at 110°C, ketone IIc (yield 40%) and the initial Ic (9%) were preparatively isolated. 9-Methyl-3,6-dibromocarbazole (IIe), compounds Ia, IIa, and carbazole were detected by mass spectrometry, indicating the occurrence of competing processes of dehalogenation and subsequent halogenation of the substrate, as in the case of the iodo derivative Id. If it is assumed that the dehalogenation is a slow stage, while the subsequent formation of the dihalo derivative proceeds rapidly, then the value of the dehalogenation/trifluoroacetylation ratio, found from the relative intensities of the corresponding peaks of M^+ (Table 1) and equal to 0.11 (for Ic) and 12.5 (for Id), can be used to evaluate the relative rate of acylation and dehalogenation in each case. In the reaction of compound Ic with the acylating agent, trifluoroacetylation predominates, while in the case of the iodo derivative Id, the main path of the reaction is dehalogenation of the substrate, and deiodination is ~100 times more rapid than debromination.

EXPERIMENTAL

The electronic spectra were run on a SF-16 spectrophotometer in DCE. The IR spectra were recorded on a UR-20 spectrophotometer in mineral oil, while the PMR spectra were taken on a Tesla BS-487c spectrometer (80 MHz) in $CDCl_3$, using HMDS as internal standard. The mass spectra were obtained on a MX-1310 spectrometer with a direct system of sample introduction, and energy of ionizing electrons of 20 eV. The course of the reaction was controlled by TLC on Silufol plates. The reaction mixtures were separated by column chromatography on grade II activity Al_2O_3.

9-Methyl-3-trifluoroacetyl-6-chlorocarbazole (IIb). A 1.3 ml portion (9 mmoles) of $(CF_3CO)_2O$ and 0.7 ml (9 mmoles) of CF_3CO_2H are added to a solution of 0.717 g (3 mmoles) of compound Ib in 3 ml of DCE, and the mixture is heated in a sealed ampule for 8 h at 110°C. The solvent is distilled off, and the resinous residue is extracted by 50 ml of boiling hexane. When the mixture is cooled, 0.66 g (63.3%) of ketone IIb separates from the extract, mp 115.5-116.5°C (from hexane), R_f 0.32 (hexane—benzene—DCE, 3:6:1). IR spectrum: 1700 (C=O), 1235-1130 (C—F), 800, 765, 730, 675 cm^{-1} (C—H). PMR spectrum: 3.69 (3H, s, N—CH_3); 7.27-7.60 (2H, m, 1-, 8-H); 8.10-8.43 (3H, m, 2-, 7-, 4-H); 8.75 ppm (1H, s, 5-H). Found, %: C 58.0, H 2.8, Cl 11.0, F 18.4, N 4.5; M^+ 311, 313. $C_{15}H_9ClF_3NO$. Calculated, %: C 57.8, H 2.8, Cl 11.4, F 18.3, N 4.5. The compound obtained is identical with a sample prepared by chlorination of ketone IIa.

Trifluoroacetylation of 9-Methyl-3-chlorocarbazole by a $(CF_3CO)_2O$:CF_3CO_2H (10:1) Mixture. A 4.0 g portion (19 mmoles) of compound Ib is dissolved in 15 ml of DCE, 8 ml of the acylating mixture are added, and the mixture is heated in a sealed ampule for 8 h at 110°C. The mixture is then evaporated and separated on a column (3 × 50 cm), eluting with 350 ml of a hexane—benzene (1:1) mixture, recovering 1.64 g of unreacted carbazole Ib (41.5%). The elution is continued with a hexane—ether (1:1) mixture, and by collecting 10-ml portions, 1.26 g (22%) of ketone IIb and 0.7 g of an unseparable mixture of two compounds with R_f 0.63 and 0.56 are washed out from the column. The mixture is treated with 20 ml of acetone, the precipitate is filtered, crystallized from 10 ml of benzene to yield 0.53 g (8%) of 1,1,1-tris(9-methyl-3-chloro-6-carbazolyl)-2,2,2-trifluoroethane (IV), mp 306-307°C (from benzene), R_f 0.56. IR spectrum: 1600 (C=C), 1220-1140 (C—F), 300, 740, 665 cm^{-1} (C—H). Found, %: C 67.0, H 3.6, Cl 14.4, F 7.3, N 1.8. M^+ 723, 725, 727, 729. $C_{41}H_{27}Cl_3F_3N_3$. Calculated, %: C 67.0, H 3.7, Cl 14.7, F 7.9, N 1.9.

The acetone filtrate, obtained after separation of compound IV, is evaporated to dryness, the residue is recrystallized from 5 ml of hexane to yield 93 mg (1.6%) of 9-methyl-1-trifluoroacetyl-6-chlorocarbazole (V), mp 133.5-134.5°C, R_f 0.63. IR spectrum: 1690 (C=O), 1570 (C=C), 1220-1330 (C—F), 800, 745, 730, 650 cm^{-1} (C—H). PMR spectrum: 3.59 (3H, s, N—CH_3); 7.0-7.50 (3H, m, arom.); 7.75-8.0 (2H, m, 4-, 5-H); 8.13 ppm (1H, d, J = 7 Hz, 2-H). Found, %: C 57.6, H 2.9, Cl 11.1, F 18.0, N 4.5; M^+ 311, 313. $C_{15}H_{19}ClF_3NO$. Calculated: C 57.8, H 2.8, Cl 11.4, F 18.3, N 4.5.

1,1,1-Tris(9-methyl-3-chloro-6-carbazolyl)-2,2,2-trifluoroethane (IV). A 0.15-ml portion (2 mmoles) of CF_3CO_2H is added to a solution of 0.52 g (2.4 mmoles) of compound Ib and 0.4 g (1.2 mmole) of ketone IIb in 3 ml of DCE, and the solution is left to stand at 20°C for 10 h. The finely crystalline precipitate is filtered, washed with 10 ml of cold acetone and after recrystallization from 5 ml of benzene, 0.31 g (33%) of compound IV is obtained, which is identical with a sample obtained in the preceding experiment.

Trifluoroacetylation of 3-Iodo-9-methylcarbazole (Id). A 2.5-ml portion of a $(CF_3CO)_2O$:CF_3CO_2H (5:1) mixture is added to a solution of 1.66 g (5.4 mmoles) of compound Id in 8 ml of DCE, and the mixture is heated in a sealed ampule for 4 h at 110°C. The mixture is cooled, the precipitate is filtered, and crystallized from 5 ml of acetone to yield 0.5 g (22%) of diiodo derivative IIf, that is identical with the compound described in [5].

The dichloroethane filtrate is washed with water, dried over $CaCl_2$, and separated on a column (2 × 50), eluting with a hexane—benzene (1:1) mixture. Yield 0.14 g (6.4%) of ketone IId, mp 179-179.5°C (from hexane), R_f 0.17. IR spectrum: 1695 (C=O), 1250-1120 (C—F), 800, 760, 730, 656 cm^{-1} (C—H). PMR spectrum: 3.71 (3H, s, N—CH_3); 7.0-7.38 (2H, m, 1-, 8-H), 7.5-7.75 (1H, d, $J_{1,2}$ = 7 Hz, 2-H); 8.0-8.23 (1H, d, $J_{7,8}$ = 7 Hz, 7-H); 8.30 (1H, s, 4-H); 8.60 ppm (1H, s, 5-H). Found, %: C 44.6, H 2.4, F 14.0, N 3.5; M^+ 403. $C_{14}H_9F_3NO$. Calculated, %: C 44.7, H 2.2, F 14.4, N 3.5. The product is identical with the compound obtained by the iodination of ketone IIa by the method described in [5].

3,6-Diiodo-9-methylcarbazole (IIf). A 0.5-ml portion (6.5 mmoles) of CF_3CO_2H is added to a solution of 0.307 g (1 mmole) of compound Id in 2 ml of DCE, and the mixture is left to stand for 1 h at 20°C. The precipitate is filtered, and after recrystallization from 5 ml of acetone, 86 mg (20%) of compound IIf are obtained. In addition, in the mass spectrum of the reaction mixture there are peaks of M^+ with m/z 360, 486, and 612 (Table 1), which probably belong to the products of an oxidative combination of compounds Ia,d, and are 3,3'-dicarbazyls, containing 0, 1, and 2 iodine atoms, respectively.

3-Bromo-9-methyl-6-trifluoroacetylcarbazole (IIc). A 6.3-ml portion of the $(CF_3CO)_2O$: CF_3CO_2H (1:1) mixture is added to a solution of 4.0 g (15 mmoles) of the bromo derivative Ic in 10 ml of DCE, and the mixture is heated in a sealed ampule for 6 h at 110°C. The mixture is then evaporated and the residue is separated on a column (3 × 50 cm), eluting with 350-ml of a hexane–benzene (1:1) mixture. Thus, 0.55 g (9%) of the initial bromo derivative Ic and 2.2 g (40%) of ketone IIc are isolated. Mp 139-140°C (from hexane), R_f 0.32 (hexane–ether, 1:1). IR spectrum: 1695 (C=O), 1240-1140 (C–F), 810, 770, 735, 665 cm^{-1} (C–H). Found, %: C 50.4, H 2.3, F 16.0, N 4.0; M^+ 355, 357. $C_{15}H_9BrF_3NO$. Calculated, %: C 50.6, H 2.3, F 16.0, N 3.9.

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RESEARCH ON IMIDAZO[1,2-a]BENZIMIDAZOLE DERIVATIVES.

25.* REACTION OF 2,9-DISUBSTITUTED IMIDAZO[1,2-a]BENZIMIDAZOLES WITH ACRYLIC ACIDS AND THEIR DERIVATIVES

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The substitutive addition of acrylic acids and their esters, amides, and nitriles to 2,9-disubstituted imidazo[1,2-a]benzimidazoles, which leads to 3-(imidazo[1,2-a]benzimidazol-3-yl)propionic acids and their derivatives, was studied. The rate of addition depends on the structure of the unsaturated compound, the nature of the substituent in the 2 position, the magnitude of the π charge on the carbon atom in the 3 position of the heteroring, and the reaction conditions. The addition proceeds most smoothly in polyphosphoric acid (PPA). In the case of acrylonitrile imidazo[1,2-a]benzimidazol-3-ylpropionic acid amides were isolated in PPA. In the reaction of α- or β-substituted acrylic acids with 2-phenylimidazo[1,2-a]benzimidazoles in PPA, in addition to the corresponding imidazo[1,2-a]benzimidazol-3-ylpropionic acids, products of their intramolecular cyclodehydration at the ortho position of the phenyl substituent are formed.

Two types of reactions with electrophilic olefins, viz., 1,4-cycloaddition and substitutive addition, are known for π-electron-surplus heteroaromatic systems [2]. Condensed systems with a common nitrogen atom are also classified as π-surplus systems [3], but for them, de-

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[*] See [1] for Communication 24.

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