

C-HYDROXYALKYLATION OF N-ADAMANTYLANILINES BY HEXAFLUOROACETONE
AND METHYL TRIFLUOROPYRUVATE

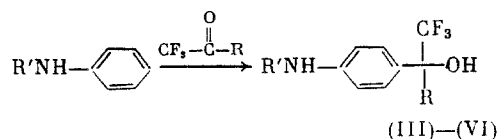
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N-(1-Adamantyl)-4-(1-hydroxy-1-trifluoromethyl-2,2,2-trifluoroethyl)aniline (III) and *N*-(1-adamantyl)-4-(1-hydroxy-1-methoxycarbonyl-2,2,2-trifluoroethyl)aniline (IV) were obtained by the reaction of *N*-(1-adamantyl)aniline with ketone (I) and ketoester (II). Analogous procedures gave *N*-(2-adamantyl)-4-(1-hydroxy-1-trifluoromethyl-2,2,2-trifluoroethyl)aniline (V) and *N*-(2-adamantyl)-4-(1-hydroxy-1-methoxycarbonyl-2,2,2-trifluoroethyl)aniline (VI). The action of hydrogen peroxide on (III) in the presence of sodium tungstenate gave *N*-(1-adamantyl)-4-(1-hydroxy-1-trifluoromethyl-2,2,2-trifluoroethyl)aniline *N*-oxide (VII).

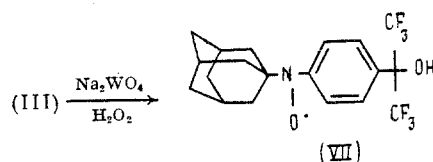
N-Alkylanilines undergo C⁴-hydroxyalkylation by hexafluoroacetone (I) under mild conditions [1]. In the present work, we studied the reaction of ketone (I) and methyl trifluoropyruvate (II) with 1- and 2-*N*-(adamantyl)anilines, whose derivatives hold interest as compounds with possible psychotropic activity [1, 2].

The reaction of *N*-(1-adamantyl)aniline with ketone (I) and ketoester (II) in Freon-113 at 20°C leads to *N*-(1-adamantyl)-4-(1-hydroxy-1-trifluoromethyl-2,2,2-trifluoroethyl)aniline (III) and *N*-(1-adamantyl)-4-(1-hydroxy-1-methoxycarbonyl-2,2,2-trifluoroethyl)aniline (IV) in high yield (Table 1). *N*-(2-Adamantyl)aniline reacts similarly to form C⁴-hydroxyalkylation products (V) and (VI).



R' = 1-adamantyl, R = CF₃ (III), R = COOCH₃ (IV); R' = 2-adamantyl, R = CF₃ (V), R = COOCH₃ (VI).

We studied the capacity of these products to form nitroxyl radicals. The action of hydrogen peroxide on (III) in the presence of sodium tungstenate in aqueous methanol gives stable crystalline nitroxyl radical (VII) isolated in 53% yield. The stability of (VII) is attributed to the bulky α-hydroxyhexafluoroisopropyl group in the para-position of the phenyl ring, which hinders recombination and subsequent disproportionation of the nitroxyl [3].



Products (III)-(VII) were obtained as stable, analytically pure crystalline products (Table 1). The structures of (III)-(VI) were established by ¹H and ¹⁹F NMR spectroscopy (Table 2). The EPR spectrum of (VII) is a multiplet with a_N = 12.1 Oe and a_H(ortho) = 2.9 Oe.

TABLE 1. Properties of (III)-(VII)

Compound	Yield, %	Mp, °C	R_f	Calculated, % Found			Chemical formula
				C	H	N	
(III)	89	180-181	0,58	58,01 57,82	5,34 5,21	3,56 3,54	$C_{19}H_{21}F_6NO$
(IV)	70	140-141	0,5	62,66 62,29	6,26 6,14	3,65 3,60	$C_{20}H_{24}F_3NO_3$
(V)	64	148-150	0,7	58,01 58,00	5,32 5,12	3,56 3,35	$C_{19}H_{21}F_6NO$
(VI)	62	96-98	0,82	62,66 62,54	6,26 6,25	3,65 3,53	$C_{20}H_{24}F_3NO_3$
(VII)	53	150-151	-	55,88 55,51	4,90 4,90	3,41 3,29	$C_{19}H_{20}F_6NO_2$

TABLE 2. 1H and ^{19}F NMR Spectral Data of Products in Acetone- d_6

Compound	δ , ppm						
	H^2	H^6	H^3	H^5	Adamantyl	OCH_3	^{19}F
(III)	6,75 d		7,4 d		1,8 m	-	-2,86 ^s
(IV)	6,75 d		7,25 d		1,8 m	3,8 s	-1,38 ^s
(V)	6,65 d		7,4 d		1,8 m		-2,9 ^s
(VI)	6,62 d		7,4 d		1,8 m	3,8 s	-1,4 ^s

EXPERIMENTAL

The 1H and ^{19}F NMR spectra of the products were obtained at 20°C on a Bruker R-200 spectrometer at 200.12 and 188.31 MHz, respectively. The chemical shifts were determined relative to TMS as the internal standard for the 1H NMR spectra and to CF_3CO_2H as the external standard for the ^{19}F NMR spectra. The EPR spectra were taken on a Varian E-104 spectrometer. The R_f values of the products were obtained on Silufol UV-254 plates using 6:1 CCl_4 -acetone as the eluent. The spots were detected using UV light.

N-(1-Adamantyl)-4-(1-hydroxy-1-trifluoromethyl-2,2,2-trifluoroethyl)aniline (III). A sample of 0.9 g N-(1-adamantyl)aniline in 10 ml Freon-113 was placed in a sealed vessel and cooled to from -60 to -50°C. Then, 1 g (I) was condensed into the vessel, which was then maintained at constant 20°C for 24 h. After cooling, the vessel was opened. The precipitate formed was filtered and washed with pentane to give 1.36 g (III).

N-(1-Adamantyl)-4-(1-hydroxy-1-methoxycarbonyl-2,2,2-trifluoroethyl)aniline (IV). A sample of 0.9 g N-(1-adamantyl)aniline in 10 ml Freon-113 was placed into a sealed vessel and cooled to -50°C. Then, 0.64 g (III) was added. The vessel was maintained at constant 20°C for 24 h. The precipitate formed was filtered off and washed with pentane to give 1 g (IV).

N-(2-Adamantyl)-4-(1-hydroxy-1-trifluoromethyl-2,2,2-trifluoroethyl)aniline (V) was obtained from 2.37 g N-(2-adamantyl)aniline in 15 ml Freon-113 and 2 g (I) under the conditions for the synthesis of (III). Crystallization from pentane gave 2.51 g (V).

N-(2-Adamantyl)-4-(1-hydroxy-1-methoxycarbonyl-2,2,2-trifluoroethyl)aniline (VI) was obtained from 2 g N-(2-adamantyl)aniline in 15 ml Freon-113 and 1.5 g (II) under the conditions for the synthesis of (IV). Crystallization from pentane gave 2 g (VI).

N-(1-Adamantyl)-4-(1-hydroxy-1-trifluoromethyl-2,2,2-trifluoroethyl)aniline N-oxide (VII). A sample of 0.2 g $Na_2WO_4 \cdot 2H_2O$ and 1 ml 30% hydrogen peroxide were added to 1 g N-(1-adamantyl)aniline in 30 ml methanol and maintained for seven days at 20°C. The methanolic solution was diluted with an equal volume of water and extracted with chloroform. The combined chloroform extracts were dried over $MgSO_4$. The mother liquor was evaporated to dryness to give 0.55 g bright orange, crystalline (VII).

LITERATURE CITED

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