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POLYFLUORINATED NITRILE OXIDES

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(2+3)-Cycloaddition of polyfluorinated aliphatic nitrile oxides, generated in situ, to donor dipolarophiles takes place regioselectively to give the 5-substituted isoxazolines, and is limited by the donor and steric properties of the dipolarophiles.

The polyfluorinated nitrile oxides which have so far been obtained in situ and characterized by (2+3)-cycloaddition are trifluoroacetonitrile [1-3], 2-hydrotetrafluoropionitrile [4], and perfluorobenzonitrile oxides [5]. The properties of these compounds differ in many respects from their nonfluorinated analogs, benzonitrile and acetonitrile oxides [6].

We have now examined (2+3)-cycloadditions of 2,2-dihydrotrifluoropropionitrile oxide (I), 2-hydrotetrafluoropropionitrile oxide (II) (for preliminary communication, see [4]), and 2-hydrohexafluoroisobutyronitrile oxide (III).

Oxides (I-III) are usually generated by dehydrohalogenation of the appropriate hydroxyamoyl fluorides (IVa-c), chlorides (IVd, e), or bromides (IVf-h).

$$I Va R=H, X=F; b R=F, X=F; c R=CF_3, X=F; c R=F, X=CI; e R=CF_3, X=CI; f R=H, X=Br; g R=F, X=Br; h R=CF_3, X=Br$$

In this case, the hydroxamoyl fluorides (IVa-c) could not be converted into the oxides (I-III) or their concerted cycloaddition products [7].

However, dehydrochlorination of the hydroamoyl chlorides (IVd, e) takes place even under mild conditions (at -40 to -55°C with triethylamine in ether or other inert solvents). In the presence of vinyl butyl ether at -20°C, 5-butoxy-3-polyfluoroalkyl-1,2-oxazolines (Va) (40%) and (Vb) (23%) were obtained, showing that the oxides (II) and (III) were generated in situ. The spectral data and chromatography showed that the 5-butoxy derivatives (Va) and (Vb) were formed exclusively.

The structures of the oxazolines (Va) and (Vb) were also confirmed by their conversion into the isoxazoles (VIa) and (VIb) by heating in sulfuric acid, as in the case of other 5-alkoxy-1,2-oxazolines [1, 6].



Va R=F; b $R=CF_3$; c R=H; VI a R=F; b $R=CF_3$

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The most convenient precursors for the nitrile oxides (I-III) are the hydroxamoyl bromides (IVf-h), which react with triethylamine at -78°C, and in the presence of vinyl butyl ether at -20 to 0°C afford high yields of the 1,2-oxazolines (Va) (70%), (Vb), and (Vc). Subsequently, (2+3)-cycloadditions of the oxides (I-III) were carried out under conditions which were optimal in most cases, namely, the oxides were generated from the hydroxamoyl bromides (IVf-h) in ether at -15 to -10°C in the presence of the dipolarophiles.

Reactions of the oxides (I-III) with unconjugated alkenes are governed by the dipolar properties of the latter, and the yields of cycloadducts, greatest with vinyl butyl ether, are substantially lower with allyl bromide and vinyl acetate.



VII, VIII, XII a R=H, b R=F, C R=CF₃, IX-XI R=F; VIIa-c R¹=CH₂Br, VIIIa-c R¹=OAc, IX \tilde{R}^1 =CH₃, X R¹=Ph, XI R¹=C(O)CH₃, XIIa-c R¹=C(O)OC₂H₅; IX R²=CH₃, when not given \tilde{R}^2 =H

Steric hindrance in the transition state has a considerable adverse effect on ring formation in these systems. For example, the yield of the isoxazoline (IX) from the door isobutylene is lower than from monosubstituted alkenes with lower donor properties.

Reactions with conjugated dipolarophiles were examined for the most part with the oxide (II), and usually proceeded more smoothly than with unconjugated dipolarophiles. Reaction of the oxide (II) with styrene proceeds regioselectively to give the 5-substituted cyclo-adduct (X), corresponding to the minimum steric hindrance in the transition state. Satisfactory yields are also obtained with weak donors (methyl vinyl ketone and ethyl acrylate).

It is noteworthy that the yields of adducts decrease as the electron-acceptor properties of the polyfluoroalkyl groups in (I-III) increase, the cycloadducts (XI) and (XIIa-c) being formed as a single regioisomer, whereas the reactions of nonfluorinated nitrile oxides with such dipolarophiles are nonregiospecific.

The adverse effect of steric factors manifests itself in the low yield of the adduct (XIII) from the oxide (II) and N-methylbenzaldimine, although the latter is one of the most reactive dipolarophiles in its reactions with unfluorinated nitrile oxides.

The weak donor properties of acetylenes, and the low propensity to conjugation, are reflected in their extremely low reactivity towards the oxides (I-III). The reactions with allene, vinylacetylene, and perfluoro-2-butyne do not give identifiable products, as in the reactions with other electrophilic dipolarophiles, polyfluoroalkenes, polyfluoroketones and their imines, and derivatives of fumaric and maleic acids. The formation of the cycloadduct (XIV) has been detected in low yield in the case of phenylacetylene only.



(2+3)-Cycloadditions of the polyfluorinated nitrile oxides (I-III) differ considerably from those of their hydrocarbon analogs, in the following ways: 1) the reactivity of the polyfluorinated nitrile oxides is determined by the donor properties of the dipolarophile, decreasing as the latter is reduced, showing the preferred binding effect of the LUMO of the 1,3-dipole and the HOMO of the dipolarophile. This is confirmed by the total regioselectivity of the (2+3)-cycloadditions of the oxides (I-III), as in the case of electrophilic hydrocarbon nitriles [6], 2) steric hindrance in the transition state has been found to have a marked effect on the outcome of the reaction, 3) the yields of the products of cycloaddition of nitrile oxides (I-III) are in all instances reduced as the electron-acceptor properties of the polyfluoroalkyl group in the 1,3-dipolarophile fragment is increased. This may be rationalized by, on the one hand a decrease in reactivity as the steric effect of the substituent increases, with a proportional decrease in the energies of the HOMO and LUMO in the series (I-III). On the other hand, the electrophilic properties of the 1,3-dipoles and their affinity for halide ion increase in the same series, i.e., there is an increasing

Com- pound	Chemical shift, ppm	Coupling const., Hz		
IVf	-14,1 (3F, t, CF ₃); 3,4 (2H, q, CH ₂); 7,3 (1H, s, OH)	J _{FH} =9,8		
IV g	-1.3 (3F, d.d., CF ₃); 120,1 (1F, d.q. α -F); 5,3 (1H, d.q. α -H); 8,9 (1H, s. OH)	$J_{\rm FF} = 14.0; \ J_{\rm CF_3H} = 5.5;$		
IVħ	$-12,8$ (6F, d, CF ₃); 4,2 (1H, sept, α -H); 10,3 (1H, br Ω H)	$J_{\rm FH} = 7.4$		
Vъ	-12.9 (6F, d, CF ₃); 4.3 (1H, sept, 3-H); 3.0 (2H, m, 4-H); 5.6 (1H, d.d. 5-H); 3.6 (2H, m, OCH ₂); 14 (4H, m, CH ₂ (H)); 0.8 (3H, t, 5-CH ₂)	$J_{\rm FH} = 8.0; J_{45} = 5.0; J_{45} = 2.8; J_{\rm CH_3CH_2} = 5.5$		
Vc	-14,0 (3F, t, CF ₃); 3.0 (2H, q, 3-CH ₂); 2.6 (2H, m, 4-H); 3.3 (1H, d, d 5-H); 3.5 (2H, m, OCH ₂); 1.3 (4H, m, CH); 0.6 (3H, t, 5-CH)	$J_{\rm FH} = 11.0; J_{45} = 6.5; J_{45} = 3.0; J_{\rm CH_3CH_2} = 5.0$		
Vla	1,6 (3F, \mathbf{d} - \mathbf{d} , (CF ₃); 121.8 m (1F, m, α -F); 5.8 (1H, \mathbf{d} - \mathbf{d} , (CF ₃); 121.8 m (1F, m, α -F); 5.8 (1H, \mathbf{d} - d	$J_{FF} = 14.3; J_{FII} = 6.0;$		
VIb	-11.3 (6F, d, CF ₃); 4.5 (1H, sept, 3-CH); 6,4 (1H, d, 4-H); 8.5 (1H, d, 5-H)	$J_{\rm FH} = 44.0; \ J_{45} = 1.0$ $J_{\rm FH} = 8.0; \ J_{45} = 2.0$		
VIIa	-14.4 (3F, t. CF ₃); 3.1 (2H, q, 3-CH ₂); 2.9 (2H, m, 4-H); 4.7 (1H, m, 5-H); 3.3 (2H, d, CH ₂ Br)	$J_{\rm FH} = 15,0; \ J_{\rm CHCH_2Br} = 5,4$		
VIIЪ*	-1.0 (3F, d, d, CF ₃); -0.9 (3F, d, d, CF ₃); 125,9 (1F, m, α -F); 5,5 (1H, d, g, 3-H); 3,1 (2H, m, d, H); 4 (2H, d, G, H); 3,4 (2H, m, d, H); 4 (2H, d, G, H); 5 (4, CH, d, H); 5 (4, CH, H); 5 ($J_{FF} = 14.2; J_{FH} = 6.2; J_{FH} = 44.0; J_{CHCH_2Br} = 5.0$		
VIIc	-12.8 (6F, d, CF ₃); 4.2 (1H, sept. 3-H); 3.1=(2H, -12.8 (6F, d, CF ₃); 4.2 (1H, sept. 3-H); 3.1=(2H, -12.8 (2H d, CH Br)	$J_{\rm FH} = 8,7; \ J_{\rm CHCH_2Br} = 5,0$		
VIIIa	-13.7 (3F, t, CF ₃); 3.1 (2H, q 3-H); 3.0 (2H, m.	$J_{\rm FH} = 11,5; \ J_{45} = 6,1;$		
VIIIb*	-0.3 (3F, d.d. CF_3); -0.2 (3F, d. d CF_3); 127,0 (1H, m α -F); 3.1 (2H, m 4-H); 6.6 (1H, d.d.	$J_{45} = 2.5$ $J_{FF} = 14.7; J_{FH} = 6.0;$ $J_{FH} = 44.0; J_{45} = 5.7;$		
VIIIc	5-H); 1,8 (3H, s, CH_3); 5,5 (1H, d, q, 3-H) -12,2 (6F, d, CF_3); 4,3 (1H, sept. 3-H); 3,0 (2H,	$J_{45} = 2,6$ $J_{FH} = 8,5; J_{45} = 7,2;$		
IX	m, 4-H); 0,9 (1H, d, d, 5-H); 1,7 (0H, S, CH ₃) 0.3 (3F, d, CF ₃); 126,0 (1F, d, q, α -F); 5,6 (1H, d, q, 3-H); 2,8 (2H, m, 4-H); 1,3 (6H, S, CH ₃)	$J_{45} = 2,2$ $J_{FF} = 15,5; J_{FH} = 6,0;$ $J_{Gem FH} = 45,0$		
X*	-0.9 (3F, d, d, CF ₃); -0.8 (3F, d, d CF ₃); 126.0 (1F, d, q, α -F); 5.6 (1H, d, q, 3-H); 3.2 (2H, m 4-H); 5.6 (1H, d, d, 5-H); 7.27.4 (5H, m, Ph)	$J_{FF} = 15,5; J_{FH} = 6,4;$ $J_{em FH} = 45,0; J_{45} = 4,0;$ $J_{45} = 4,0;$		
XI*	-0.5 (3F, d.d. CF ₃): -0.6 (3F, d.d. CF ₃): 126.4 (1F, m, α -F); 5.4 (1H, d. q. 3-H); 3.1 (2H, m, 4.H): 4.9 (1H, m. 5-H): 2.1 (3H s. CH ₃)	$J_{FF} = 14.5; J_{FH} = 6.2; J_{gem} = 45.0$		
XII.a	-13,5 (3F, t. CF ₃); 3.0 (2H, q. 3-H); 3.0 (2H, d. 4-H); 4.7 (1H, t. 5-H); 3.8 (2H, q. OCH ₂); 0.9 (3H + 5-CH ₂)	$J_{\rm FH} = 10,3; J_{45} = 9,5; J_{\rm CH_3CH_2} = 7,0$		
XII Þ*	-0.5 (3F, d.d. CF ₃); -0.6 (3F, d.d. CF ₃); 126,1 (1F, m, α -F); 5.6 (d.q. 3-H); 3.4 (2H, m, 4-H); 5,1 (1H, m, 5-H); 4.1 (2H, q. OCH ₂); 1.2 (2H, t. 5,CH ₂)	$J_{FF} = 15,2; J_{FH} = 6,0;$ $J_{em FH} = 44,5;$ $J_{CH_3CH_2} = 7,2$		
XIIe	-12.5 (3F, d, CF ₃); 4.2 (1H, sept. 3-H); 3.1 (2H, d, 4-H); 4.9 (1H, t, 5-H); 3.9 (2H, q, OCH ₂); 1.0 (2H, t, 5-CH)	$J_{\rm FH} = 8.5; J_{45} = 9.7; J_{\rm CH_3CH_2} = 8.0$		
XIII	(511, α 5-C113) -2.2 (3F, m, CF ₃); 127.2 (1F, m, α -F); 5.6 (1H, m, 3-H); 2.5 (3H, br., s, NCH ₃); 5.9 (1H, m, 5-H); 7.4	—		
XIV	(31, m, Fi) 0.0 (3F, d,d. CF ₃); 120,0 (1F, m, α -F); 5.8 (1H, d,q, 3-H); 6.6 (1H, s, 4-H); 7,37,7 (5H, m, Ph)	$J_{FF} = 15.0; J_{FH} = 6.4;$ $J_{gem FH} = 44.4$		

TABLE 1. ¹⁹F and ¹H NMR Spectra of Products Obtained

*The two sets of signals in the ¹⁹F NMR spectra correspond to diastereoisomers.

tendency to undergo oligomeric S_N2 reactions. The outcome of these reactions is apparently determined by these two factors, and 4) the cycloaddition of the polyfluorinated nitrile oxides (I-III), like nonfluorinated oxides, takes place via an aromatic transition state. This is shown by the enhanced reactivity of these 1,3-dipoles towards conjugated dipolarophiles.

EXPERIMENTAL

NMR spectra were obtained in $CDCl_3$ on a Hitachi R-20 instrument (¹H 60 MHz, ¹⁹F 56.46 MHz), from an internal standard (TMS) and an external standard (CF₃COOH) respectively. IR spectra were obtained on a Perkin-Elmer R-225 in thin layers on KBr.

The properties of the products obtained are given in Tables 1 and 2. The elemental analyses of all the compounds for C, H, F, and N were in agreement with the calculated values. Compounds (Va), (IX), (X), and (XIIb) have been reported previously in [4], (IVb-e) in [7], and (IVa-c) in [8].

Com- pound	Empirical formula	bp,°C (hPa)	n _D ²⁰	á 4 ²⁰	IRspec	others	Yield, %
IV f	C3H3BrF3NO	64 (24)	1,4233	1,8071	1615	29003500	
IV g	[C ₃ H ₂ BrF ₄ NO] ₄ (C ₂ H ₅) ₂ O	64 (60)	1,4040	1,7425	1610	29003450	
IVh	[C ₄ H ₂ BrF ₆ NO] ₄ (C ₂ H ₅) ₂ O	67 (50)	1,3802	1,7034	1615	2050 3500	
Vb Vc VIa VIb VIIa VIIb VIIc VIIC VIIIa VIIIc IX X	$\begin{array}{c} C_{10}H_{13}F_{6}NO_{2}\\ C_{9}H_{14}F_{3}NO_{2}\\ C_{5}H_{3}F_{4}NO\\ C_{6}H_{3}F_{6}NO\\ C_{6}H_{7}B_{7}F_{3}NO\\ C_{6}H_{6}B_{1}F_{4}NO\\ C_{7}H_{6}B_{1}F_{6}NO\\ C_{7}H_{6}F_{6}NO_{3}\\ C_{7}H_{7}F_{4}NO_{3}\\ C_{8}H_{7}F_{6}NO_{3}\\ C_{7}H_{7}F_{6}NO_{3}\\ C_{7}H_{7}F_{6}NO_{3}\\ C_{7}H_{9}F_{4}NO\\ C_{11}H_{9}F_{4}NO\\ \end{array}$	$\begin{array}{c} 70 & (8) \\ 84 & (5) \\ 110 \\ 118 \\ 60 & (2,7) \\ 49 & (2,7) \\ 84 & (13) \\ 82 & (2,7) \\ 60 & (2,7) \\ 60 & (2,7) \\ 88 & (16) \\ 60 & (33) \\ 84 & (1,3) \end{array}$	1,3772 1,4027 1,3621 1,3489 1,4410 1,4200 1,3980 1,4100 1,3890 1,3750 1,3694 1,4670	$\begin{array}{c} 1,3118\\ 1,1813\\ 1,3602\\ 1,4830\\ 1,6606\\ 1,6826\\ 1,7429\\ 1,3096\\ 1,4282\\ 1,4944\\ 1,3050\\ 1,3381 \end{array}$	1605 1610 1655 1610 1615 1610 1615 1615	(011) 1750 (C=C) 1760 (C=C) 1750 (C=O) 1745 (C=O) 1740 (C=O) 16501710	58 88 78 56 38 31 49 32 30 28 33
XI XII a XII b XII c XII c XIII XIV	C7H7F4NO2 C8H10F3NO3 C8H9F4NO3 C9H9F4NO3 C9H9F6NO3 C11H10F4N2O C11H7F4NO	84 (20) 82 (2,7) 84 (2,7) 82 (19) 80 (2,7) 70 (2,7)	1,3920 1,4100 1,4004 1,3843 1,4700 1,4680	1,4511 1,3096 1,3908 1,4430 1,3251 1,3058	1615 1615 1615 1610 * †	$\begin{array}{c} (Ph) \\ 1715 (C=0) \\ 1730 (C=0) \\ 1735 (C=0) \\ 1730 (C=0) \\ 1730 (C=C) \end{array}$	50 63 57 37 24 14

TABLE 2. Properties of Compounds Obtained

*1580-1660 cm⁻¹ (C=N), (Ph). †1620-1700 cm⁻¹ (C=N), (Ph).

Hydroxamoyl Bromides (IVf, g, h).* Hydrogen bromide was bubbled through a solution of 0.1 mole of the appropriate hydroxamoyl fluoride (IVa, b, or c) in 15 ml of dry ether at -60°C to saturation, the mixture kept for two days at -78°C, then warmed to $\sim 20^{\circ}$ C and fractionated in vacuo. The hydroxamoyl bromides (IVg, h) were isolated as their 4:1 complexes with ether.

<u>5-Butoxy-3-polyfluoroalky1-1,2-oxazolines (Va, b)</u>. To a mixture of 20 mmole of triethylamine and 20 mmole of binyl butyl ether in 30 ml of dry ether was added dropwise with stirring at -20°C 20 mmole of the appropriate hydroxamoyl chloride (IVd, e), and the mixture kept for 16 h at -20 to 10°C, warmed to 20°C, filtered, and the filtrate fractionated in vacuo.

<u>3-Polyfluoroalkyl-1,2-oxazoles (VIa, b)</u>. To 15 mmole of the oxazoline (Va or b) was added at 0°C 5.0 ml of 96% sulfuric acid, and the mixture kept for 24 h at \sim 20°C. It was then evaporated under reduced pressure, and fractionated at atmospheric pressure.

Oxazolines (Va-c), (VIIa-c), (VIIIa-c), (IX-XI), (XIIa-c), (XIII), and (XIV). To a mixture of 20 mmole of the appropriate hydroxamoyl bromide (IVf-h) and 20 mmole of the dipolarophile in 30 ml of dry ether was added slowly with stirring at -15°C 20 mmole of triethylamine. The mixture was kept for 10-20 h at this temperature, then warmed to 20°C, filtered, and the filtrate fractionated in vacuo.

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*Synthesized here by the method described in [8].