Oxazolidones from Hexafluoroacetone and Sodium Cyanide

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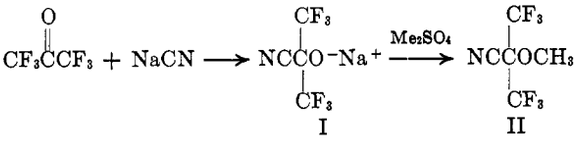
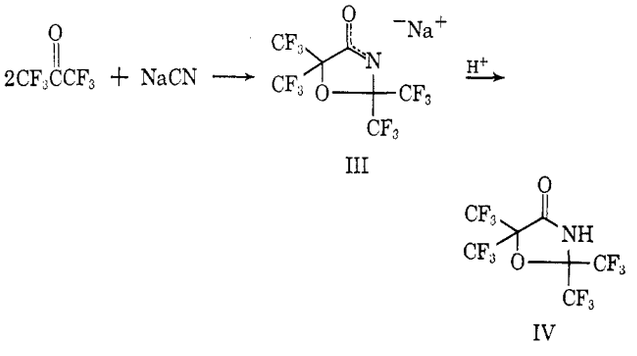
Hexafluoroacetone forms with sodium cyanide a 2:1 adduct which is the sodium salt of 2,2,5,5-tetrakis(trifluoromethyl)-4-oxazolidone. This product is an ambident anion and can be alkylated on either oxygen or nitrogen.

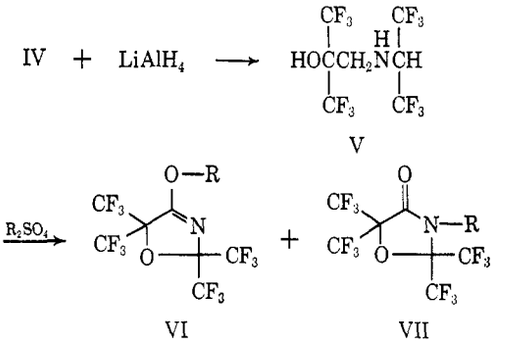
The reaction of hexafluoroacetone with sodium cyanide has been reported to give a stable, ether-soluble adduct (I), which can be converted to the cyanohydrin of hexafluoroacetone upon acidification.[1] We have confirmed these results by repeating the reaction in acetonitrile and have prepared the methyl ether (II) by alkylation of this adduct with methyl sulfate.



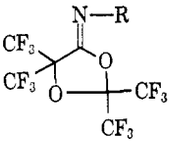
In addition to this 1:1 adduct, we have found that hexafluoroacetone also forms a soluble 2:1 adduct with sodium cyanide if an excess of the ketone is employed. Upon acidification, the 2:1 adduct gives a high yield of the oxazolidone (IV). This oxazolidone is sufficiently acidic to dissolve in dilute bicarbonate solution. It is quite resistant to both acidic and basic hydrolysis. It survives both boiling 10% sodium hydroxide solution and boiling concentrated hydrochloric acid solution.



Structure IV of the 2:1 adduct was verified by the F^{19} nmr spectrum which shows two kinds of fluorine in equal amount, the infrared spectrum which shows a lactam carbonyl at 5.62 μ, and reductive degradation. Reduction of IV with lithium aluminum hydride gave the amine (V), which suggests that the nitrogen atom is in the ring of the adduct and not in an exocyclic imino group. Structure IV was further confirmed by a series of alkylation experiments. As expected, III is an ambident anion. Alkylation with ethyl sulfate gave 47% O alkylation (VI, R = Et) and 53% N alkylation (VII, R = Et). Neither of these products is identical with the isomeric iminodioxolane VIII (R = Et)[2] prepared from hexafluoroacetone and ethyl isocyanide; thus



the imino structure (VIII, R = H) for the 2:1 adduct is ruled out.



Alkylation of anion III with methyl sulfate gave predominantly the N-methyl derivative (VII, R = CH_3) with only a trace amount of the O-methyl derivative (VI, R = CH_3). The reason for this rather remarkable difference in alkylation behavior between ethyl and methyl sulfate is not known. Steric effects may be partially responsible. Since the oxygen atom should be more accessible than the nitrogen atom, it may be preferentially alkylated by the more bulky alkylation agent. Other effects, such as the larger SN1 character in alkylation reactions with ethyl sulfate compared with methyl sulfate, may also increase the proportion of attack on the more electronegative oxygen atom.[3] Although alkylation of the anion III with methyl sulfate gave only a small yield of the O-alkylated product, this material (VI, R = CH_3) could be prepared in good yield by reaction of the free oxazolidone (IV) with diazomethane.

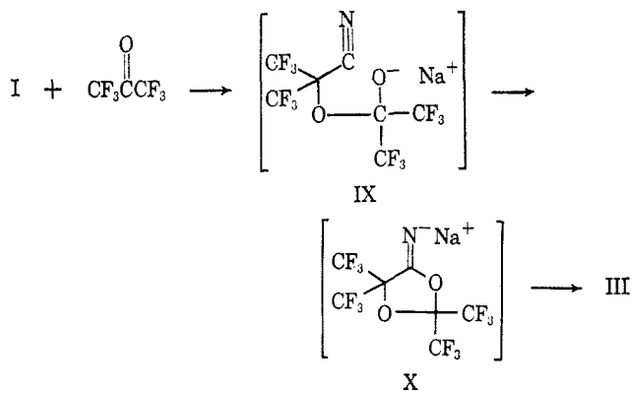
We have postulated the following series of reactions to explain the formation of the oxazolidone (IV). First, a cyanide ion adds to hexafluoroacetone to give a salt of the cyanohydrin (I). Anion I then adds to more ketone to give the unstable intermediate anion (IX), which cyclizes to the iminodioxolane anion (X). Anion X then undergoes a Chapman rearrangement[4] to

(1) T. Mills, J. O. Rodin, R. M. Silverstein, and C. Woolf, *J. Org. Chem.*, **29**, 3715 (1964).

(2) W. J. Middleton, D. C. England, and C. G. Krespan, *ibid.*, **32**, 948 (1967).

(3) E. S. Gould, "Mechanism and Structure in Organic Chemistry," Henery Holt and Co., New York, N. Y., 1960, p 297. The effects of increasing degree of "SN1" character on substitution reactions of ambident nucleophiles is discussed.

(4) R. Roger and D. Neilson, *Chem. Rev.*, **61**, 190 (1961).



give the anion III, which can be stabilized by delocalization of the charge over both nitrogen and oxygen. This series of reactions is related to those reported by Russian investigators,[5] who have postulated that an iminodioxolane is an intermediate in the formation of an oxazolidone from the reaction of a cyanohydrin of an aromatic aldehyde with hexafluoroacetone.

Experimental Section[6]

3,3,3-Trifluoro-2-methoxy-2-trifluoromethylpropionitrile (II).—Hexafluoroacetone (25 ml at −78°, *ca.* 40 g, 0.24 mole) was slowly distilled into a stirred suspension of 20 g (0.4 mole) of sodium cyanide in 75 ml of acetonitrile. The reaction mixture was warmed to 70° and most of the solid dissolved. Dimethyl sulfate (51 g, 0.4 mole), was added over a period of 1 hr, and the mixture was stirred overnight. Water was added until all of the solid dissolved, and the lower organic phase was separated, washed with 5% sodium bicarbonate and then water, and dried over anhydrous magnesium sulfate. Distillation gave 36.5 g (74%) of 1,1,1-trifluoro-2-methoxy-2-trifluoromethyl-2-propionitrile as a colorless liquid: bp 59–60°, $n^{25}D$ <1.3. The fluorine and proton nmr spectra both showed a single, unsplit resonance band. The infrared spectrum contained a band at 4.44 μ for C≡N.

Anal. Calcd for $C_5H_3F_6NO$: C, 29.00; H, 1.46; F, 55.10; N, 6.77. Found: C, 30.85; H, 1.81; F, 55.03; N, 7.06.

This same reaction was run in benzonitrile solvent to give a slightly higher yield (83%) of product. Benzonitrile can be removed from the product more easily than acetonitrile because of its higher boiling point.

The product was further characterized by hydrolysis to the amide. A stirred mixture of 5 g of 3,3,3-trifluoro-2-methoxy-2-trifluoromethylpropionitrile and 25 ml of concentrated sulfuric acid was heated on a steam bath until the reaction mixture was homogeneous (about 3 hr). The mixture was cooled and poured into 100 ml of crushed ice. The white solid that formed was collected on a filter and recrystallized from pentane. There was obtained 2.5 g of 3,3,3-trifluoro-2-methoxy-2-trifluoromethylpropionamide as colorless needles, mp 60–61°.

Anal. Calcd for $C_5H_5F_6NO_2$: C, 26.67; H, 2.24; F, 50.65; N, 6.22. Found: C, 26.29; H, 2.66; F, 50.52; N, 5.98.

2,2,5,5-Tetrakis(trifluoromethyl)-4-oxazolidone (IV).—Hexafluoroacetone (100 ml at −78°, *ca.* 1 mole) was slowly distilled over a period of 30 min into a stirred suspension of 24.5 g (0.5 mole) of sodium cyanide in 300 ml of acetonitrile. The reaction mixture warmed to 60° during the addition. The mixture was cooled and mixed with 200 ml of concentrated hydrochloric acid. The organic layer was separated, washed with water, and distilled. There was obtained 143 g (80%) of 2,2,5,5-tetrakis(trifluoromethyl)-4-oxazolidone as a colorless distillate (bp 160–165°) that solidified to a white solid (mp 102–105°) upon cooling. Recrystallization from benzene gave 119 g of colorless needles: mp 106–107°, infrared at 5.62 μ. The F^{19} nmr spectrum in acetone solution showed two septets (J = 5.4 cps) at 72.9 and 78.4 ppm.

Anal. Calcd for $C_7HF_{12}NO_2$: C, 23.41; H, 0.28; F, 63.49; N, 3.90. Found: C, 23.74; H, 0.49; F, 63.13; N, 4.10.

Reduction of 2,2,5,5-Tetrakis(trifluoromethyl)-4-oxazolidone.—A solution of 35.9 g (0.1 mole) of 2,2,5,5-tetrakis(trifluoromethyl)-4-oxazolidone in 50 ml of ether was added dropwise over a period of 30 min to a stirred solution of 5.0 g of lithium aluminum hydride in 100 ml of ether. The reaction mixture was heated to reflux for 20 hr and then cooled to 0°. The excess hydride was decomposed by adding successively 5 ml of water, 5 ml of 15% aqueous sodium hydroxide, and 15 ml of water. The mixture was stirred for 2 hr and then filtered. The filtrate was distilled to give 4.65 g of N-[2,2,2-trifluoro-1-(trifluoromethyl)ethyl]-3,3,3-trifluoro-2-(trifluoromethyl)-2-hydroxypropylamine (V) as a colorless liquid: bp 140–140.5°, $n^{25}D$ 1.3140. The proton nmr spectrum showed a singlet (area 1) at τ 5.60 for OH, a doublet (J = 7.5 cps, area 2) at 6.85 for CH_2, a multiplet (area 1) at 6.50 for $C(CF_3)_2H$, and a broad multiplet (area 1) at 7.9 for NH. After exchange with D_2O, the spectrum simplified to a singlet (area 2) at τ 6.85 (uncoupled CH_2) and a septet (J = 7 cps) at 6.50. The F^{19} nmr spectrum showed a doublet and a singlet of equal area.

Anal. Calcd for $C_7H_5F_{12}NO$: C, 24.22; H, 1.45; F, 65.68; N, 4.04. Found: C, 24.59; H, 1.71; F, 65.78; N, 4.21.

2,2,5,5-Tetrakis(trifluoromethyl)-3-methyl-4-oxazolidone (VII, R = CH_3).—Hexafluoroacetone (125 ml at −78°, 1.2 moles) was distilled over a period of 30 min into a stirred suspension of 30 g (0.6 mole) of sodium cyanide in 500 ml of acetonitrile. The reaction mixture warmed to 50° during the addition. The mixture was cooled to 25°, 126 g of dimethyl sulfate was added, and the resulting mixture was stirred for 18 hr. Water was added to dissolve the precipitated salts, and the organic layer was separated, washed with water, and dried over anhydrous magnesium sulfate.

Distillation gave 190 g (85% yield) of 2,2,5,5-tetrakis(trifluoromethyl)-3-methyl-4-oxazolidone as a colorless oil: bp 135–136°, $n^{25}D$ 1.3218, infrared at 5.60 μ. The F^{19} nmr spectrum showed two septets centered at 74.6 and 77.1 ppm. The proton nmr spectrum showed a singlet at τ 6.75 with a width at half-height of 3.2 cps. Gas chromatographic analysis indicated that the sample was contaminated with 3% of the isomeric 2,2,5,5-tetrakis(trifluoromethyl)-4-methoxy-3-oxazoline, identified by comparison of retention time and infrared analysis with those of an authentic sample.

Anal. Calcd for $C_8H_3F_{12}NO_2$: C, 25.75; H, 0.81; F, 61.11; N, 3.78. Found: C, 26.22; H, 1.22; F, 60.82; N, 4.22.

Reduction of 2,2,5,5-Tetrakis(trifluoromethyl)-3-methyl-4-oxazolidone.—A solution of 37.3 g (0.1 mole) of 2,2,5,5-tetrakis(trifluoromethyl)-3-methyl-4-oxazolidone in 40 ml of ether was added dropwise to a stirred solution of 5.0 g of lithium aluminum hydride in 140 ml of ether. The reaction mixture was heated to reflux for 20 hr and then cooled to 0°. The excess hydride was decomposed by adding successively 5 ml of 15% aqueous sodium hydroxide and 15 ml of water. The mixture was stirred for 2 hr and then filtered, and the filtrate was distilled. There was obtained 8.55 g of 2,2,5,5-tetrakis(trifluoromethyl)-3-methyl-3-4-hydroxyoxazolidine as a colorless liquid (bp 148.5–150°) that solidified to a white solid (mp 49–51°) on cooling. The infrared spectrum showed bands at 2.77 and 2.87 μ for OH. The proton nmr spectrum showed a singlet at τ 7.20 (area 3) and broad doublets at 6.75 (J = 7 cps, area 1) and 4.78 (J = 7 cps, area 1). Exchange with D_2O removed the τ 6.75 peak and converted the 4.78 peak to a singlet. The F^{19} nmr spectrum showed four complex multiplets of equal area in the CF_3 region.

Anal. Calcd for $C_8H_5F_{12}NO_2$: C, 25.61; H, 1.35; F, 60.78; N, 3.74. Found: C, 25.89; H, 1.51; F, 60.01; N, 3.41.

Alkylation of 2,2,5,5-Tetrakis(trifluoromethyl)-4-oxazolidone with Diazomethane.—A 2.5% solution of diazomethane in ether was added portionwise to a solution of 17.95 g (0.05 mole) of 2,2,5,5-tetrakis(trifluoromethyl)-4-oxazolidone in 25 ml of ether until a faint, yellow color persisted. Distillation gave a colorless oil: bp 128–136°, $n^{25}D$ 1.3111.

Anal. Calcd for $C_8H_3F_{12}NO_2$: C, 25.75; H, 0.81; F, 61.11; N, 3.78. Found: C, 26.17; H, 1.08; F, 60.87; N, 3.52.

Gas chromatographic analysis indicated that the product was a mixture of two components in the ratio 65:34. The more abundant component, 2,2,5,5-tetrakis(trifluoromethyl)-4-me-

(5) Yu. V. Zeifman and N. P. Gambaryan, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1622 (1964); *Bull. Acad. Sci. USSR Div. Chem. Sci.*, 1531 (1964).

(6) Fluorine nmr spectra were obtained with a Varian Associates high-resolution spectrometer operating at 56.4 Mcps. Spectra were calibrated in terms of higher field displacement in parts per million (ppm) from the F^{19} resonance of trichlorofluoromethane. Proton spectra were obtained on a Varian A-60 spectrometer.

thoxy-3-oxazoline (VI, R = CH_3), was separated by preparative gas chromatography and obtained as a colorless solid: mp 30°, infrared at 5.95 μ. The proton nmr spectrum showed a singlet at τ 5.81 (in $CDCl_3$) with a width at a half-height of 0.8 cps. The F^{19} nmr spectrum showed two septets centered at 73.9 and 78.5 ppm.

Anal. Calcd for $C_8H_3F_{12}NO_2$: C, 25.75; H, 0.81; F, 61.11; N, 3.78. Found: C, 25.61; H, 1.15; F, 60.49; N, 3.69.

The less abundant component was identified as 2,2,5,5-tetrakis(trifluoromethyl)-3-methyl-4-hydroxyoxazolidone by comparison of its infrared spectrum and gas chromatographic retention time with those of an authentic sample.

2,2,5,5-Tetrakis(trifluoromethyl)-3-ethyl-4-oxazolidone (VII, R = Et) and 2,2,5,5-Tetrakis(trifluoromethyl)-4-ethoxy-3-oxazoline (VI, R = Et).—Hexafluoroacetone (125 ml at −78°, 1.2 moles) was distilled over a period of 30 min into a stirred suspension of 30 g (0.6 mole) of sodium cyanide in 500 ml of acetonitrile. The reaction mixture warmed to 50° during the addition. The mixture was cooled to 25°, 150 g of diethyl sulfate was added, and the resulting mixture was stirred for 18 hr. Water was added to dissolve the precipitated salts, and the organic layer was separated, washed with 5% sodium bicarbonate solution and then with water, and dried over anhydrous magnesium sulfate. Distillation gave 147 g (61%) of a colorless oil: bp 140–141°, $n^{25}D$ 1.3234.

Anal. Calcd for $C_9H_5F_{12}NO_2$: C, 27.93; H, 1.30; F, 58.88; N, 3.62. Found: C, 28.42; H, 1.59; F, 58.71; N, 3.78.

Gas chromatographic analysis indicated the product was a mixture of two components in the ratio of 47:53. The components were separated by preparative gas chromatography for further characterization.

2,2,5,5-Tetrakis(trifluoromethyl)-4-ethoxy-3-oxazoline, the minor component, was obtained as a colorless oil: bp 136°, $n^{25}D$ 1.3178, infrared at 5.98 μ. The proton nmr spectrum showed a quartet (J = 7 cps) at τ 5.38 of area 2 and a triplet (J = 7 cps) at 8.57 of area 3. The F^{19} nmr spectrum showed two septets centered at 73.9 and 78.4 ppm.

Anal. Found: C, 28.03; H, 1.50; F, 58.72; N, 3.75.

2,2,5,5-Tetrakis(trifluoromethyl)-3-ethyl-4-oxazolidone, the major component, was obtained as a colorless oil: bp 142°, $n^{25}D$ 1.3263, infrared at 5.65 μ. The proton nmr spectrum showed a quartet (J = 7 cps) at τ 6.28 of area 2 and a triplet (J = 7 cps) at 8.65 of area 3. The F^{19} nmr spectrum showed two septets centered at 74.6 and 77.1 ppm.

Anal. Found: C, 28.08; H, 1.55; F, 58.78; N, 3.75.

Reaction of Silver Salt of 2,2,5,5-Tetrakis(trifluoromethyl)-4-oxazolidone with Ethyl Iodide.—Hexafluoroacetone (21 ml at −78°, 0.1 mole) was distilled into a stirred suspension of 4.9 g (0.1 mole) of sodium cyanide in 100 ml of acetonitrile. A solution of 17.0 g (0.1 mole) of silver nitrate in 25 ml of acetonitrile was added, and the sodium nitrate that precipitated was collected on a filter. Ethyl iodide (15.6 g, 0.1 mole) was added to the solution of the silver salt. An exothermic reaction ensued, and a precipitate formed. The reaction mixture was allowed to stand for 20 hr and then filtered. Distillation of the filtrate gave 25 g of a colorless oil: bp 140–141°, $n^{25}D$ 1.3280. Infrared, proton nmr, and gas chromatographic analyses showed this product to consist of an approximately 50:50 mixture of 2,2,5,5-tetrakis(trifluoromethyl)-3-ethyl-4-oxazolidone and 2,2,5,5-tetrakis(trifluoromethyl)-4-ethoxy-3-oxazoline.

Sodium Salt of 2,2,5,5-Tetrakis(trifluoromethyl)-4-oxazolidone (III).[7]—Hexafluoroacetone (42 ml at −78°, *ca.* 0.4 mole) was slowly distilled into a stirred suspension of 9.8 g (0.2 mole) of sodium cyanide in 200 ml of acetonitrile. The reaction mixture was cooled to 25° and filtered. The filtrate was evaporated to dryness under reduced pressure. There was obtained 72 g of the sodium salt of 2,2,5,5-tetrakis(trifluoromethyl)-4-oxazolidone as a white powder, mp 165–175° dec, infrared at 6.0 μ.

Anal. Calcd for $C_7F_{12}NNaO_2$: Na, 6.30. Found: Na, 6.36.

Registry No.—Hexafluoroacetone, 684-16-2; sodium cyanide, 143-33-9; II, 7770-94-7; 3,3,3-trifluoro-2-methoxy-2-trifluoromethylpropionamide, 7775-62-4; IV, 7730-28-1; V, 7730-29-2; 2,2,5,5-tetrakis(trifluoromethyl)-3-methyl-4-hydroxyoxazolidone, 7730-31-6; VI, R = CH_3, 7730-32-7; VI, R = Et, 7730-33-8; VII, R = CH_3, 7730-30-5; VII, R = Et, 7730-34-9; sodium salt of 2,2,5,5-tetrakis(trifluoromethyl)-4-oxazolidone, 7770-95-8.

(7) J. D. Warnell has found that potassium cyanide reacts with excess hexafluoroacetone in the absence of solvent, even at −78°, to give the potassium salt of the oxazolidone.

The Reaction of Isocyanates with *o*-Hydroxy Aromatic Aldehydes. Condensations of 3,4-Dihydro-4-hydroxy-3-alkyl-2H-1,3-benzoxazin-2-ones with Compounds Having Active Hydrogen

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3,4-Dihydro-3-alkyl-2H-1,3-benzoxazin-2-ones (type **1**), 4,4′-oxobis(3,4-dihydro-3-alkyl-2H-benzoxazin-2-ones) (type **3**), and 1-(3,4-dihydro-3-alkyl-2-oxo-2H-1,3-benzoxazin-4-yl-1,3-dialkylureas (type **2**) were obtained by the condensation of *o*-hydroxy aromatic aldehydes with alkyl isocyanates. Type **1** condenses readily with compounds having active hydrogen to give 4-substituted 3,4-dihydro-3-alkyl-2H-1,3-benzoxazin-2-ones (type **8**). Ring opening to carbamates and other chemical transformations of compounds of type **8** (borohydride reduction of ketones, condensation of diketones with diamines to give quinoxalines) are described.

The base-catalyzed condensation of *o*-hydroxy aromatic aldehydes with equimolar quantities of aliphatic isocyanates in ether has been reported[1] to give compounds of type **1a**, and with 2 moles of isocyanate to give type **1b**. In the case of aromatic isocyanates, only type **1b** was obtained (see Chart I).

As part of a basic research program to develop new syntheses of novel heterocyclic compounds, we have independently studied this reaction (generally under somewhat different conditions) and found that condensation of *o*-hydroxy aromatic aldehydes with 2 moles of aliphatic isocyanates in tetrahydrofuran or benzene at refluxing temperature gave compounds of type **1a** (*ca.* 15%), **2** (*ca.* 30%), and a dimeric material (**3**), the latter being a major product (*ca.* 45–50%). Under similar reaction conditions, phenyl isocyanate gave the N-phenyl analog of **3** in 50% yield. Compounds of type **3** prepared by this method are listed in Table I. The structure of type **3** compounds was based on elemental analyses, Rast molecular weight determinations, infrared, and proton magnetic resonance spectral studies, plus additional chemical evidence discussed below.

The infrared absorption spectra (Nujol mulls) of these compounds show absence of OH and NH func-

(1) R. E. Strube and F. A. MacKellar, *Rec. Trav. Chim.*, **83**, 1191 (1964).