## ALIPHATIC FLUORO NITRO COMPOUNDS

#### COMMUNICATION 3. FLUORINE-CONTAINING NITRO ALCOHOLS AND NITRO ETHERS

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Aliphatic fluorine-containing nitro alcohols have been prepared previously by the condensation of perfluorinated aldehydes and ketones with nitro compounds in presence of potassium carbonate [1, 2]. In this investigation we have shown that fluorine-containing nitro alcohols can be readily prepared from the aliphatic fluoro nitro compounds that we have synthesized [3]. Thus, by the reaction of 1,1,1-trifluoro-2-nitroethane (I) with aqueous formaldehyde at 0° in presence of alkali 2-nitro-2-(trifluoromethyl)-1,3-propanediol (II) is formed in yields of up to 95%.

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$$\begin{array}{c} CH_2OH\\ CF_3 - CH_2 - NO_2 + 2CH_2O \xrightarrow[NaOH]{} CF_3 - C - NO_2\\ (I) & CH_2OH (II) \end{array}$$

Under these conditions 1,1,1,2-tetrafluoro-2-nitroethane (III) also reacts readily with formaldehyde with formation of 2,3,3,3-tetrafluoro-2-nitro-1-propanol (IV).

$$\begin{array}{c} CF_3 - CFH - NO_2 + CH_2O \xrightarrow[NaOH]{} CF_3 - CF - NO_2 \\ \downarrow \\ CH_2OH \\ (III) & (IV) \end{array}$$

Rise in the reaction temperature lowers the yield of the nitro alcohol considerably, particularly in the case of trifluoronitroethane; this is due to the low stability of a vicinal fluoro nitro compound in an alkaline medium. Thus, when titrated with 0.1 N NaOH at  $20^{\circ}$  1,1,1-trifluoro-2-nitroethane is broken down completely with the elimination of all three fluorine atoms. At  $0^{\circ}$ , however, trifluoronitroethane readily dissolves in 0.1 N NaOH, and on cautious acidification of the solution the compound is regenerated in 90-95% yield.

We also studied the behavior of fluoronitroalkanes under the conditions of the Mannich reaction. It was found that vicinal fluoro nitro compounds react vigorously with formaldehyde solution and an amine even at  $-10^{\circ}$ ; reaction is accompanied by partial decomposition of the fluoro nitro compounds, and in attempts to isolate individual products by distillation explosive decomposition was observed. In an acid medium no reaction was observed even at temperatures of 80-100°. However, when a mixture of 1,1,1-trifluoro-2-nitroethane, paraform, an amine hydrochloride, and an alcohol was heated we unexpectedly obtained a 3-alkoxy-1,1,1-trifluoro-2-nitropropanes:

$$\begin{array}{c} \mathrm{CF}_{3} - \mathrm{CH}_{2} - \mathrm{NO}_{2} + (\mathrm{CH}_{2}\mathrm{O})_{x} + (\mathrm{C}_{2}\mathrm{H}_{5})_{2} \mathrm{NH} \cdot \mathrm{HCl} + \mathrm{ROH} \rightarrow \mathrm{CF}_{3} - \mathrm{CH} - \mathrm{NO}_{2} \\ (\mathrm{I}) & & | \\ \mathrm{CH}_{2}\mathrm{OR} \\ (\mathrm{V}) & \mathrm{R} = \mathrm{CH}_{3}; \\ (\mathrm{VI}) & \mathrm{R} = \mathrm{C}_{2}\mathrm{H}_{5}; \\ (\mathrm{VII}) & \mathrm{R} = \mathrm{C}_{3}\mathrm{H}_{7} \end{array}$$

The structure of the products was confirmed by their infrared spectra. The antisymmetric and symmetric stretching vibrations of the  $NO_2$  group of the alkoxytrifluoronitropropanes are at 1590 and 1335 cm<sup>-1</sup> respectively, which is characteristic for a secondary nitro group. Alkoxytrifluoronitropropanes give a clear qualitative test for a secondary nitro group with nitrous acid. Finally, the alkoxytrifluoronitropropanes were reduced over Raney nickel to the corresponding 1-(alkoxymethyl)-2,2,2-trifluoroethylamines (VIII):

$$\begin{array}{c} \mathrm{CF}_{3}-\mathrm{CH}-\mathrm{NO}_{2} & \xrightarrow{[H]} & \mathrm{CF}_{3}-\mathrm{CH}-\mathrm{NH}_{2} \\ & | \\ & \mathrm{CH}_{2}\mathrm{OR} & & | \\ & \mathrm{CH}_{2}\mathrm{OR} & & \mathrm{CH}_{2}\mathrm{OR} \end{array}$$

$$(\mathrm{VIII})$$

It has been shown recently that alkoxymethylation under the conditions of the Mannich reaction is observed for compounds containing a mobile hydrogen attached to nitrogen. When maleic hydrazide or saccharine is heated with paraform, a secondary amine hydrochloride, and an alcohol, the corresponding N-alkoxymethylene derivatives are formed [4, 5].

We made a detailed study of the condensation of fluoronitroalkanes with formaldehyde under various conditions. It was found that 1,1,1-trifluoro-2-nitroethane reacts neither with an aqueous solution of formaldehyde nor with a solution of formaldehyde and alcohol, whether the medium be neutral or acid. 1,1,1-Trifluoro-2-nitroethane does not react with paraform and an amine hydrochloride when heated in dioxane. Alkoxymethylation is observed only in presence of a considerable amount of secondary amine hydrochloride, although this is recovered completely from the reaction. Thus, with molar proportions of trifluoronitroethane, paraform, and diethylamine hydrochloride of 1:1:1 reaction is complete at 100° in ten hours, and 3-ethoxy-1,1,1-trifluoro-2-nitropropane (VI) is obtained in 80% yield. When the amount of diethylamine hydrochloride is reduced to one-tenth this amount with other conditions the same, the yield of (VI) falls to 16%. Tertiary amine salts, e.g., triethylamine hydrochloride, do not catalyze the alkoxymethylation reaction. As was expected, when alcohol was replaced by water alcohols were obtained instead of ethers. Thus, when 1,1,1-trifluoro-2-nitroethane (I) and 1,1,1,2-tetrafluoro-2-nitroethane (III) were heated with paraform and diethylamine hydrochloride in water we obtained 3,3,3-trifluoro-2-nitro-1-propanol (IX), 2-nitro-2-(trifluoromethyl)-1,3-propanediol (II), and 2,3,3-tetrafluoro-2-nitro-1-propanol (IV).

$$CF_{3} - CH_{2} - NO_{2} + (CH_{2}O)_{x} + (C_{2}H_{5})_{2} NH \cdot HCl + H_{2}O \rightarrow (I) \qquad CH_{2}OH \rightarrow CF_{3} - CH - NO_{2} + CF_{3} - C - NO_{2} \rightarrow (ILI) CH_{2}OH (II) \qquad CH_{2}OH (II) \qquad CH_{2}OH (II) \qquad CF_{3} - CFH - NO_{2} + (CH_{2}O)_{x} + (C_{2}H_{5})_{2} NH \cdot HCl + H_{2}O \rightarrow CF_{3} - CF - NO_{2} \rightarrow (III) \qquad CH_{2}OH (IV)$$

We did not succeed in extending alkoxymethylation under the conditions of the Mannich reaction to other compounds containing mobile hydrogen. Thus, malonic ester, acetoacetic ester, nitrocyclohexane, nitroethane, 1-fluoro-2-nitroethane, and 1-chloro-1-fluoro-2-nitroethane do not react with paraform and an amine hydrochloride in an alco-hol. Moreover, 3-alkoxy-1,1,1-trifluoro-2-nitropropanes do not under go further alkoxymethylation, though the re-maining hydrogen is extremely mobile. Nitroform reacts with a mixture of formaldehyde, amine hydrochloride, and alcohol even at 20°, but 2,2,2-trinitroethanol is then formed in 87% yield.

The mechanism of the alkoxymethylation of trifluoronitroethane may be represented as follows. In the reaction between trifluoronitroethane and formaldehyde and secondary amine hydrochloride the usual Mannich salt (X) is formed. In an acid medium this compound is unstable and breaks down to the original reactants, as is seen when trifluoronitroethane, paraform, and diethylamine hydrochloride are heated in dioxane. However, in presence of an alcohol at an elevated temperature the nucleophilic replacement of  $NR_2 \cdot HCl$  by OR occurs.

$$CF_{3} - CH_{2} - NO_{2} + (CH_{2}O)_{x} + R_{2}NH \cdot HCl \simeq CF_{3} - CH - NO_{2} \xrightarrow{\text{ROH}} CF_{3} - CH - NO_{2}$$

$$I$$

$$CH_{2}NR_{2} \cdot HCl \xrightarrow{\text{CH}} CH_{2}OR$$

$$(X)$$

# EXPERIMENTAL

<u>2-Nitro-2-(trifluoromethyl)-1,3-propanediol (II)</u>. A solution of 1 g of NaOH in 10 ml of water was added in the course of two hours at 0° with stirring to a mixture of 38.7 g of 1,1,1-trifluoro-2-nitroethane and 100 ml of 20% aqueous formaldehyde solution. The mixture was then acidified and extracted with ether continuously for six hours. The ethereal solution was dried over anhydrous magnesium sulfate, ether was evaporated, and we obtained 54 g (95%) of 2-nitro-2-(trifluoromethyl)-1,3-propanediol, m. p. 140-142° (from a mixture of alcohol and heptane). Infrared

spectrum: symmetric and antisymmetric stretching vibrations of the nitro group at 1340 and 1575 cm<sup>-1</sup>. Found: C 25.35, 25.51; H 3.17, 3.12; F 30.28, 30.48; N 7.53, 7.48%.  $C_4H_6F_3O_4N$ . Calculated: C 25.47; H 3.20; F 30.16; N 7.41%.

<u>5-Nitro-2-phenyl-5-(trifluoromethyl)-m-dioxane.</u> A mixture of 5 g of (II), 2.8 g of benzaldehyde, 0.05 g of p-toluenesulfonic acid, and 40 ml of benzene was boiled with a water separator for six hours. Distillation of the mixture gave 7 g of a colorless liquid of b. p. 127° (1 mm), which solidified on cooling. After recrystallization we obtained 6.62 g (90%) of 5-nitro-2-phenyl-5-(trifluoromethyl)m-dioxane, m. p. 58-59° (from heptane). Found: C 47.31, 47.70; H 3.60, 3.67; F 19.99, 20.33; N 5.31, 5.36%. C<sub>11</sub>H<sub>10</sub>F<sub>3</sub>O<sub>4</sub>N. Calculated: C 47.68; H 3.64; F 20.58; N 5.06%.

2,3,3,3-Tetrafluoro-2-nitro-1-propanol (IV). A solution of 1 g of NaOH in 5 ml of water was added to 0° with stirring to a mixture of 44 g of 1,1,1,2-tetrafluoro-2-nitroethane and 50 ml of 20% aqueous formaldehyde solution. The mixture was stirred further for three hours and then acidified; the lower layer was separated, dried over anhydrous magnesium sulfate, and distilled. We obtained 47.7 g (90%) of 2,3,3,3-tetrafluoro-2-nitro-1-propanol; b. p. 36-38° (5 mm);  $n_D^{20}$  1.3511,  $d_4^{20}$  1.5924. Symmetric NO<sub>2</sub> stretch 1315 cm<sup>-1</sup>; antisymmetric stretch 1610 cm<sup>-1</sup> [6]. Found: C 20.42, 20.45; H 1.80, 1.83; F 43.70, 43.58; N 7.81, 7.87%; MR 23.99. C<sub>3</sub>H<sub>3</sub>F<sub>4</sub>O<sub>3</sub>N. Calculated: C 20.35; H 1.70; F 42.93; N 7.92%; MR 23.76.

Its p-nitrobenzoic ester was prepared; m. p. 73-74° (from alcohol). Found: N 8.88, 8.92%.  $C_{10}H_6F_4O_6N_2$ . Calculated: N 8.62%.

<u>1,1,1-Trifluoro-3-methoxy-2-nitropropane (V)</u>. A mixture of 7.3 g of diethylamine, 10.2 ml of concentrated hydrochloric acid, 3.0 g of paraform, 12.9 g of 1,1,1-trifluoro-2-nitroethane, and 30 ml of methanol was heated in a sealed glass tube at 100° for ten hours. 100 ml of water was then added to the mixture, and the lower layer was separated, washed twice with water, dried, and distilled. We obtained 8.9 g (51.4%) of 1,1,1-trifluoro-3-methoxy-2-nitropropane; b. p. 48° (30 mm);  $n_D^{20}$  1.3580,  $d_4^{20}$  1.3370. Infrared spectrum: symmetric and antisymmetric stretching vibrations of the nitro group 1340 and 1585 cm<sup>-1</sup>. Found: C 28.01, 28.15; H 3.52, 3.55; F 33.64, 33.87%; MR 28.41. C<sub>4</sub>H<sub>6</sub>F<sub>3</sub>O<sub>3</sub>N. Calculated: C 27.78; H 3.50; F 32.96%; MR 28.35.

By evaporating the aqueous layer we obtained 8.9 g of diethylamine hydrochloride. Found: Cl 32.3, 32.1%.  $C_4H_{12}ClN$ . Calculated: Cl 32.4%.

<u>3-Ethoxy-1,1,1-trifluoro-2-nitropropane (VI)</u>. A mixture of 7.3 g of diethylamine, 10.2 ml of concentrated hydrochloric acid, 3.0 g of paraform, 12.9 g of 1,1,1-trifluoro-2-nitroethane, and 30 ml of ethanol was boiled for ten hours. The mixture was then diluted with water and extracted three times with ether. The combined ethereal solutions were dried and distilled through a column. We obtained 14.9 g (79.7%) of 3-ethoxy-1,1,1-trifluoro-2-nitropropane; b. p. 144-146°;  $n_D^{20}$  1.3634,  $d_4^{20}$  1.2564. Symmetric stretch of NO<sub>2</sub> 1335 cm<sup>-1</sup>, antisymmetric stretch 1590 cm<sup>-1</sup>. Found: C 32.08, 32.37; H 4.34, 4.34; F 30.35, 30.06%; MR 33.13; mol. wt. 184; 185. C<sub>5</sub>H<sub>8</sub>F<sub>3</sub>O<sub>3</sub>N. Calculated: C 32.12; H 4.31; F 30.46%; MR 32.97; mol. wt. 187.

A mixture of 0.01 mole of diethylamine, 10.2 ml of concentrated hydrochloric acid, 0.1 mole of paraform, 0.1 mole of 1,1,1-trifluoro-2-nitroethane, and 30 ml of ethanol was boiled for ten hours. After similar treatment (see preceding experiment) we obtained 3 g (16%) of (VI).

<u>1,1,1-Trifluoro-2-nitro-3-propoxypropane (VII)</u>. A mixture of 7.3 g of diethylamine, 10.2 ml of concentrated hydrochloric acid, 3.0 g of paraform, 12.9 g of 1,1,1-trifluoro-2-nitroethane, and 30 ml of propyl alcohol was heated at 100° for ten hours. The mixture was then diluted with 100 ml of water, and the lower layer was separated, washed three times with water, dried, and distilled through a column. We obtained 12.1 g (60%) of 1,1,1-trifluoro-2-nitro-3-propoxypropane; b. p. 47° (3 mm);  $n_D^{20}$  1.3731,  $d_4^{20}$  1.2093. Infrared spectrum: symmetric and antisymmetric stretching vibrations of the nitro group 1340 and 1580 cm<sup>-1</sup>. Found: C 35.88, 36.02; H 5.01, 5.12; F 27.28, 27.26%; MR 37.88.  $C_6H_{10}F_3O_3N$ . Calculated: C 35.83; H 5.02; F 28.36%; MR 37.59.

2-Nitro-2-(trifluoromethyl)-1,3-propanediol (II). A mixture of 11 g of diethylamine hydrochloride, 9 g of paraform, 0.5 ml of concentrated hydrochloric acid, 12.9 g of 1,1,1-trifluoro-2-nitroethane, and 60 ml of water was heated with stirring for ten hours at 100°. The mixture was then extracted five times with ether, the extract was dried with anhydrous magnesium sulfate, and ether was driven off. The crystalline residue was washed with benzene and recrystallized from a mixture of alcohol and hexane. We obtained 7 g (37%) of 2-nitro-2-(trifluoromethyl)-1,3-propanediol, m. p. 140-142°. Found: C 25.40, 25.54; H 3.27, 2.14; F 30.13, 30.65%.  $C_4H_6F_3O_4N$ . Calculated: C 25.47; H 3.20; F 30.16%.

3,3,3-Trifluoro-2-nitro-1-propanol (IX). A mixture of 22 g of diethylamine hydrochloride, 6 g of paraform, 1 ml of concentrated hydrochloric acid, 25.8 g of 1,1,1-trifluoro-2-nitroethane, and 30 ml of water was heated with stirring at 100°. The mixture was then extracted five times with ether, and the extract was dried over anhydrous magnesium sulfate and distilled. We obtained: a) 6.7 g (21%) of 3,3,3-trifluoro-2-nitro-1-propanol; b. p. 86.5-87° (20 mm);  $n_D^{20}$  1.3763,  $d_4^{20}$  1.5321. Found: F 34.84, 34.61; N 8.53, 8.53%; MR 23.83. C<sub>3</sub>H<sub>4</sub>F<sub>3</sub>O<sub>3</sub>N. Calculated: F 35.83; N 8.79%; MR 23.63. b) 3.8 g (10%) of 2-nitro-2-(trifluoromethyl)-1,3-propanediol, m. p. 139-141° (from a mixture of alcohol and heptane).

 $\underbrace{2,3,3,3-\text{Tetrafluoro-2-nitro-1-propanol (IV).}_{0.5 \text{ ml of concentrated hydrochloric acid, 14.7 g of 1,1,1,2-tetrafluoro-2-nitroethane, and 50 ml of water was stirred at 100° for 20 h. The mixture was then extracted five times with ether, and the extract was dried over an-hydrous magnesium sulfate and distilled. We obtained 15.7 g (89%) of 2,3,3,3-tetrafluoro-2-nitro-1-propanol; b. p. 37° (5 mm); n_D^{20}$  1.3513, d<sub>4</sub><sup>20</sup> 1.5918. Found: C 20.24, 20.25; H 1.83, 1.96; F 43.46, 43.27%. C<sub>3</sub>H<sub>3</sub>F<sub>4</sub>O<sub>3</sub>N. Calculated: C 20.34; H 1.70; F 42.93%.

<u>1-(Ethoxymethyl)-2,2,2-trifluoroethylamine (VIII)</u>. A mixture of 5.4 g of 3-ethoxy-1,1,1-trifluoro-2-mitropropane, 25 ml of alcohol, and 1 g of Raney nickel catalyst was introduced into a steel autoclave. The autoclave was purged with hydogen, and the hydrogen pressure was then brought to 60 atm. After 90 min the pressure of hydrogen had fallen to 50 atm; the excess of pressure was released, the autoclave was opened, and the contents were vacuum-distilled. Methanol saturated with hydrogen chloride was added to the distillate, and the mixture was vacuum-evaporated. We obtained 4.3 g (77%) of the hydrochloride of 1-(ethoxymethyl)-2,2,2-trifluoroethylamin, m. p. 176-177° (from a mixture of acetone and alcohol). Found: N 7.08, 7.14; Cl 18.5, 18.7%.  $C_5H_{11}F_3CION$ . Calculated: N 7.24; Cl 18.3%.

## SUMMARY

1. By the condensation of 1,1,1-trifluoro- and 1,1,1,2-tetrafluoro-2-nitroethanes with formaldehyde in presence of alkalies fluorine-containing nitro alcohols and diols were obtained.

2. In an acid alcoholic medium under the conditions of the Mannich reaction 1,1,1-trifluoro-2-nitroethane forms the corresponding 3-alkoxy-1,1,1-trifluoro-2-nitropropanes.

## LITERATURE CITED

- 1. D J. Cook, O. R Pierce, and E T McBee, J. Amer. Chem. Soc., 76, 83 (1954).
- 2. Ch'en Ch'ing-yün, N. P. Gambaryan, and I. L. Knunyants, Dokl. AN SSSR, 133, 1113 (1960).
- 3. I. L Knunyants, L. S. German, and I N. Rozhkov, Izv. AN SSSR, Ser. khim., 1963, 1946.
- 4. H. Feuer and R Harmetz, J. Organ. Chem., 24, 1501 (1959).
- 5. G. R Pettit and J. A. Settepani, J. Organ. Chem., 27, 1714 (1962).
- 6. V. I. Slovetskii, V. A. Shlyapochnikov, S. A. Shevelev, A. A. Faizil'berg, and S. S. Novikov, Izv. AN SSSR, Otd. Khim. N., 1961, 330.

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