SYNTHESIS OF THE CYANOHYDRIN OF METHYL PERFLUOROHEPTYL KETONE
AND REACTION OF THE KETONE WITH HYDROGEN CYANIDE

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SUMMARY

The cyanohydrin of methyl perfluoroheptyl ketone 2 was able
to be synthesized by a two-step process, i.e., an addition of
sodium bisulfite and subsequent treatment with sodium cyanide.
When equimolar amounts of ketone 2 and sodium cyanide were re-
acted in water or dipolar aprotic solvent such as dimethyl-
formamide, acetonitrile, 1,2-dimethoxyethane and tetrahydro-
furan, cyclic addition products composed of two molecules of
ketone 2 and one molecule of hydrogen cyanide were exclusively
formed as 2,5-dimethyl-2,5-bis(perfluoroheptyl)-4-oxazolidone
6 and 2,5-dimethyl-2,5-bis(perfluoroheptyl)-1,3-dioxolane-4-one
7 instead of the cyanohydrin of ketone 2. It is conceivable
that a solubility characteristic of a compound carrying a long
perfluoroalkyl group is responsible for the exclusive formation
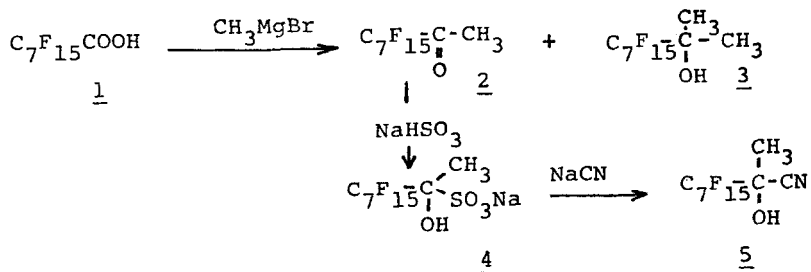of cyclic compounds 6 and 7.

INTRODUCTION

Cyanohydrins are intermediates for syntheses of acrylo-
nitriles and acrylic acid esters. So far the cyanohydrin of
methyl trifluoromethyl ketone 1 has been prepared [1] but those
of the longer perfluoroalkyl methyl ketones have not yet been
reported. In this article are described the synthesis of the
cyanohydrin of methyl perfluoroheptyl ketone 2 as an example of
a ketone with a long perfluoroalkyl group and the reaction of
the ketone with hydrogen cyanide.

RESULTS AND DISCUSSION

Methyl perfluoroheptyl ketone 2 was obtained in the re-
action of perfluorooctanoic acid with a three-fold excess of
methyl magnesium bromide in 55 % yield, and at the same time 2-
methyl-3,3,4,4,5,5,6,6,7,7,8,8,9,9,9-pentadecafluorononan-
2-ol 3 was formed in 22 % yield as by-product.

An addition reaction of hydrogen cyanide to ketone 2 was
attempted under various experimental conditions as described
later, and it seems that the cyanohydrin of ketone 2 could not
be obtained in the direct addition reaction. It is well known
that cyanohydrin of alkyl methyl ketones such as propyl methyl
ketone are prepared in a good yield by a two-step process, i.e.,
an addition of sodium bisulfite and subsequent treatment with
sodium cyanide [2,3]. The cyanohydrin of ketone 2 was found to
be synthesized successfully by this two-step process, i.e.,
ketone 2 is reacted with sodium bisulfite in water to give its
bisulfite-addition product 4 which is treated with sodium
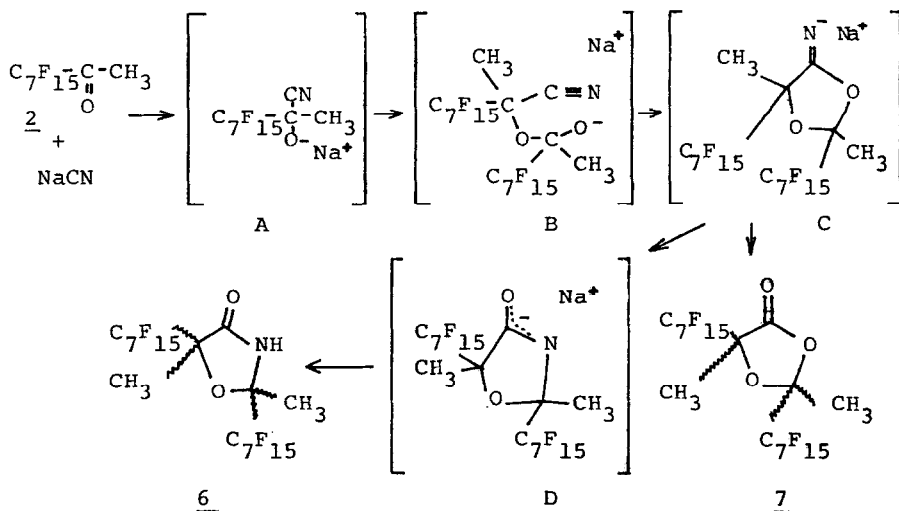cyanide to yield the cyanohydrin 5 of the ketone 2 in a good
yield.

$$C_7F_{15}COOH \xrightarrow{CH_3MgBr} C_7F_{15}\overset{\quad}{\underset{O}{C}}\text{-}CH_3 \quad + \quad C_7F_{15}\overset{CH_3}{\underset{OH}{C}}\text{-}CH_3$$

$$\underset{1}{} \qquad\qquad \underset{2}{} \qquad\qquad \underset{3}{}$$

$$\downarrow NaHSO_3$$

$$C_7F_{15}\overset{\quad CH_3}{\underset{OH}{C}}SO_3Na \xrightarrow{NaCN} C_7F_{15}\overset{CH_3}{\underset{OH}{C}}\text{-}CN$$

$$\underset{4}{} \qquad\qquad\qquad \underset{5}{}$$

It is known [1] that methyl trifluoromethyl ketone reacts
directly with hydrogen cyanide in water to yield its cyano-
hydrin. When ketone 2 was reacted with an equimolar amount of
sodium cyanide in water, the cyanohydrin of ketone 2 could not
be obtained but a white crystalline compound 6 was produced.
Elemental analysis of the compound 6 corresponded to a formula
$C_{19}H_7F_{30}NO_2$ of a compound composed of one molecule of hydrogen
cyanide and two molecules of the ketone. Its IR spectrum showed
an absorption at 1695 cm^{-1} assigned to a five-membered-ring
lactam carbonyl group [4]. Its ^{1}H NMR spectrum could not be

taken because of its insolubility in various conventional
solvents such as chloroform, acetone, dimethylsulfoxide(DMSO),
dimethylformamide(DMF), methanol and water. When an excess of
hexafluoroacetone was reacted with sodium cyanide in aceto-
nitrile, a formation of 2,2,5,5-tetrakis(trifluoromethyl)-4-
oxazolidone was reported [4] as a cyclic addition product of
one molecule of hydrogen cyanide and two molecules of hexa-
fluoroacetone instead of the cyanohydrin of hexafluoroacetone.
It was presumed therefore that compound 6 is 2,5-dimethyl-2,5-
bis(perfluoroheptyl)-4-oxazolidone.

When a 10-fold excess of sodium cyanide was reacted with
ketone 2 in water, a compound 6 only was also obtained in a 45
% yield. Moreover, when a concentrated solution of the ketone 2
in dioxane was added dropwise to equimolar amount of sodium
cyanide in water over 12 h, compound 6 only was obtained in a
60 % yield.

It is known that reaction of hexafluoroacetone with
equimolar or excess of sodium cyanide in tetrahydrofuran(THF)
[6] or acetonitrile [5] gives the cyanohydrin of hexafluoro-
acetone.   Thus, the equimolar reactions were carried out in
similar dipolar aprotic solvents such as THF, 1,2-dimethoxy-
ethane(DME), acetonitrile, DMF and DMSO. DME and THF are fully
miscible with ketone 2, while they dissolve sodium cyanide
sparingly. Thus, the reaction mixtures in these solvents consist
of two phases of solid (sodium cyanide) and liquid (ketone 2 and
solvent). Since acetonitrile, DMF and DMSO sparingly dissolve
ketone 2, reaction mixtures in these solvents are composed of
three phases of solid (sodium cyanide), liquid (ketone 2) and
liquid (solvent). The reactions in THF and DME gave a white
crystalline compound 7 in 47 and 60 % yields, respectively,
instead of compound 6. The reactions in acetonitrile gave both
compounds 6 and 7 in 2.3 % and 83 % yields, respectively. The
reactions in DMSO and DMF also gave both compounds 6 and 7 each
in 25 % yields. Elemental analysis of compound 7 corresponded
to a formula $C_{19}H_6F_{30}O_3$ of a hydrolyzed product of compound 6.
Its IR spectrum showed an absorption at 1800 cm^{-1} assigned to
five-membered-ring lactone [4]. Its ^{1}H NMR spectrum exhibited
two singlet signals with similar peak areas at 1.80 and 3.08
ppm, indicating the presence of two kinds of methyl groups.

Therefore, it was presumed that compound 7 is 2,5-dimethyl-2,5-bis(perfluoroheptyl)-1,3-dioxolane-4-one. When compound 6 was refluxed in 50 % sulfuric acid, it was converted into compound 7 quantitatively, suggesting a close relation in chemical structure between compounds 6 and 7. It is certain that the reactions of ketone 2 with hydrogen cyanide in aprotic dipolar solvents (such as THF, DME, acetonitrile, DMF and DMSO) also do not lead to cyanohydrin of ketone 2 but the cyclic addition products of two molecules of ketone 2 and one molecule of hydrogen cyanide are formed as compounds 6 and 7.

$$
\begin{array}{cccc}
C_7F_{15}\overset{\!\!\ominus}{\underset{O}{C}}\text{-}CH_3 & & & \\
\underline{2} & \rightarrow & [A] & \rightarrow [B] \rightarrow [C]
\end{array}
$$

A B C

[D] ← (from C)

6   D   7

It is probable that compounds 6 and 7 may be formed according to a similar reaction scheme as the formation of 2,2,5,5-tetrakis(trifluoromethyl)-4-oxazolidone[5] in the reaction of hexafluoroacetone with sodium cyanide. A cyanide ion adds to the carbonyl group of ketone 2 to give an anion (A) of the cyanohydrin of the ketone, which immediately adds to the carbonyl group of another molecule of ketone 2 to yield a hemiketal anion (B) of an addition product of two molecules of ketone 2 and one molecule of hydrogen cyanide. The hemiketal anion intramolecularly attacks a cyano group to yield an iminodioxolane anion (C), which then undergoes a Chapman rearrangement [7] to an oxazolidone anion (D), a neutralized product of which is compound 6. When the iminodioxolane anion (C) is hydrolyzed,

the 1,3-dioxolane-4-one 7 is formed. If the cyanohydrin anion (A) abstracts a proton from water and other molecules, the cyanohydrin should be formed.

It is known [8] that trifluoromethyl and longer perfluoro-alkyl groups such as perfluoroethyl and perfluorobutyl exert similar inductive and resonance substituent effects. Carbonyl groups of methyl trifluoromethyl ketone and methyl perfluoro-heptyl ketone 2 may thus be subjected to similar substituent effects, while the carbonyl group of hexafluoroacetone should be subjected to substituent effects twice as strong as those of methyl trifluoromethyl ketone and methyl perfluoroheptyl ketone 2. Reactions of methyl trifluoromethyl ketone [1] and hexa-fluoroacetone [5,6] with hydrogen cyanide can give their cyano-hydrins whereas methyl perfluoroheptyl ketone 2 leads to the cyclic addition compounds 6 and 7 of two molecules of ketone 2 and one molecule of hydrogen cyanide instead of the cyanohydrin 5. Therefore, it is unlikely that the electronic substituent effects of perfluoroalkyl groups are responsible for the ex-clusive formation of compounds 6 and 7 in the reaction of ketone 2 and sodium cyanide.

Hydration reactions of ketone 2, methyl trifluoromethyl ketone and hexafluoroacetone were discussed for the comparison. Ketone 2 is insoluble in water and slightly soluble in aprotic polar solvents such as DMSO and DMF. After a heterogeneous mixture of ketone 2 and deuterium oxide was stirred at room temperature for 24 h, its ^{1}H NMR spectrum exhibited only a singlet signal at 2.35 ppm as well as that of neat ketone 2. If a hydrate of ketone 2 was formed in the reaction mixture, another singlet signal due to the hydrate should appear at higher field [9]. On the other hand, methyl trifluoromethyl ketone is soluble in DMSO and DMF, and insoluble in water just after mixing. However, soon it reacts readily with water to form its hydrate in quantitative yield; this hydrate is soluble and relatively stable in water [1]. Hexafluoroacetone also re-acts easily with water to give its stable hydrate [10] which is soluble in water and boils at 57 °C at 93 mmHg. It was concluded therefore that ketone 2 is not subjected to hydration whereas methyl trifluoromethyl ketone and hexafluoroacetone are subjected to hydration.

Exclusive formation of five-membered-ring compounds 6 and 7 and no hydration of ketone 2 were supposed to be closely related to the nature of a long perfluoroheptyl group. It could be assumed that, at least, two kinds of its effects would take place such as steric hindrance and specific solubility. Perfluoroheptyl group is more bulky than trifluoromethyl group, probably causing more serious steric hindrance. In addition, because highly fluorinated organic compounds were reported to have very low solubility parameters [11] and because highly fluorinated polymers exhibit too low surface energy to be dampened with both organic and aqueous liquids [12], it may be considered that ketone 2 with a long perfluoroalkyl group should exhibit a solubility probably different from the ketones with trifluoromethyl group.

When steric hindrance effect is discussed in the reaction of ketone 2 with sodium cyanide, it is necessary to take into account both the steric addition of ketone 2 with cyanide ion and the reaction of the cyanohydrin anion (A) with another molecule of ketone 2. The latter step should be suffered from more serious steric hindrance than the former because both reacting species carry the bulky perfluoroalkyl group in the latter step, while only one reacting species has it in the former one. Actually, compounds 6 and 7 were produced exclusively, so the latter step is assumed not to suffer seriously from the steric hindrance. The bisulfite-addition product (4) of ketone 2 was obtained in a good yield, suggesting that this reaction also is not seriously influenced by steric hindrance. It is not reasonable therefore that steric hindrance of perfluoroheptyl group is a main cause for these two reactions, the exclusive formation of five-membered-ring compounds and no-hydration of ketone 2.

Next ketone 2 is discussed in terms of a solubility characteristic of a long perfluoroalkyl group. Ketone 2 is considered to be much more insoluble in water than methyl trifluoromethyl ketone and hexafluoroacetone due to perfluoroheptyl group. The former cannot form a hydrate but the latter two can. The anion (A) of the cyanohydrin of methyl perfluoroheptyl ketone 2 also is much less soluble in water and polar organic solvents than the anions of cyanohydrins of methyl trifluoromethyl ketone and hexafluoroacetone. Therefore, supposedly the latter two anions

can abstract a proton from water to give cyanohydrins while the former anion cannot meet with a water molecule but can with another molecule of ketone 2, because both species have long perfluoroalkyl groups, and react with ketone 2 to give compounds 6 and 7 exclusively.

The anion of the bisulfite-addition product of ketone 2 is considered to be more soluble in water than the cyanohydrin anion (A) because bisulfite is salt. Consequently, it can abstract a proton from water to give the bisulfite-addition product 4. Therefore, we wanted to pay attention to a solubility characteristic of a long perfluoroalkyl group for the exclusive formation of the five-membered-ring compounds 6 and 7.

EXPERIMENTAL

All melting points were uncorrected. IR and ^{1}H NMR spectra were made on a JASCO A-100 and a JEOL PMX 60$_{SI}$ instruments, respectively. Elemental analyses and molecular weight determinations were performed with a Yanaco CHN recorder MT-2 and a Knaur vapor pressure osmometer instruments, respectively.

Preparation of Methyl Perfluoroheptyl Ketone 2

To a solution of methyl magnesium bromide prepared from magnesium (7.04 g, 0.289 mol) and excess of methyl bromide in ether (200 ml) was added dropwise a solution of perfluoro-octanoic acid (40 g, 0.097 mol) in ether (50 ml) over one hour. The reaction mixture was refluxed for two hours and then poured on ice (100 g). To the mixture was added 5M hydrochloric acid (100 ml) and then the product was extracted with isopropyl ether (3 x 50 ml). The combined extracts were washed with a saturated aqueous solution of sodium chloride and dried over anhydrous magnesium sulfate. The solvent was removed and the residue was distilled to give 2 (18.8 g) and 3 (8.0 g). 2: b.p. 55-56° (20 mmHg); Analysis: Found: C, 26.50; H, 0.90%. $C_9H_3F_{15}O$ requires C, 26.23; H, 0.73%, IR(neat) 1770 cm^{-1}; NMR(CCl$_4$) 2.35 (s). 3: b.p. 83° (21 mmHg); m.p. 45°; Analysis: Found: C, 28.00; H, 1.35%. $C_{10}H_7F_{15}O$ requires C, 28.05; 1.65%; IR(neat) 3400 cm^{-1}; NMR(CDCl$_3$) 1.47 (6H, s), 2.18 (1H, s, OH).

Reaction of 2 with Sodium Bisulfite

In a 100 ml flask were placed a saturated aqueous solution of sodium bisulfite (30 ml) and 2 (22.8 g). The reaction mixture was shaken vigorously for 30 min to give a white precipitate, which was filtered off and washed with water to give 4. Compound 4 was used without drying for the preparation of compound 5. A small part of wet compound 4 was dried under reduced pressure, 4: m.p. 120° (dec). Analysis: Found: C, 20.80; H, 1.08%. $C_9H_3F_{15}O \cdot NaHSO_3$ requires C, 20.94; H, 0.78%.

Reaction of 4 with Sodium Cyanide

In a 100 ml flask were placed the wet bisulfite addition product 4 which was prepared from 22.8 g of 2, sodium cyanide (3.0 g) and water (20 ml), and the mixture was shaken vigorously for 15 min. The product was extracted with isopropyl ether (2 x 30 ml). The combined extracts were dried over magnesium sulfate. The solvent was removed under reduced pressure to give cyano-hydrin 5 (24.0 g) m.p. 67-68°; Analysis: Found: C, 27.50; H, 0.95; N, 3.50%. $C_{10}H_4F_{15}NO$ requires C, 27.35; H, 0.92; N, 3.19%. IR(KBr) 3330, 2240 cm^{-1}; NMR(CCl_2F-CF_2Cl) 1.83 (3H, s), 2.08 (1H, broad s, OH).

Reaction of 2 with Sodium Cyanide

Equimolar amounts of 2 (1-2 g) and sodium cyanide were mixed in various solvents (20 ml) and the mixtures were stirred at room temperature for 24 h. To the mixture was added 5M hydro-chloric acid until the mixture was acidic. When water or aceto-nitrile was used as solvent, the reaction gave a white crystal-line precipitate, which was filtered off and separated into fractions soluble and insoluble in acetone. The acetone-insolu-ble fractions were recrystallized from acetone and chloroform to give compounds 6 and 7, respectively. When the solvent was THF, DME, DMSO or DMF, brown-colored sticky oils were produced which were extracted with isopropyl ether, and the extract dried over magnesium sulfate, evaporated, and the material obtained was also separated into two fractions insoluble and soluble in

acetone. These two fractions were recrystallized as above method to give compounds 6 and 7. 6: m.p. 130-130.5° (acetone); Analysis: Found: C, 26.91; H, 0.97; N, 1.93%. $C_{19}H_7F_3NO_2$ requires C, 26.81; H, 0.83; N, 1.65%. IR(KBr) 1695 cm^{-1}. 7: m.p. 107.5-108° (chloroform); Analysis: Found: C, 26.85; H, 0.80%. $C_{19}H_6F_{30}O_3$ requires C, 26.78; H, 0.71%. IR(KBr) 1800 cm^{-1}; NMR(acetone d_6) 1.80 (3H, s), 3.08 (3H, s); Mw(VPO): 870.

Sulfuric Acid Catalyzed Hydrolysis of 6

A mixture of 6 (500 mg) and 50% sulfuric acid (10 ml) was refluxed for 10 h. The reaction mixture was poured on ice in a beaker, and extracted with isopropyl ether. The extract was dried over sodium sulfate, and solvent was removed under reduced pressure to give compound 7 (490 mg).

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