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The Preparation and Reactions of *N*-Substituted Hexafluoroisopropylideneimines

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N-Aryl- and *N*-alkylhexafluoroisopropylideneimines (**2**) were prepared from the hexafluorothioacetone dimer (**1**) by treatment with either aryl- or alkylamines. These imines reacted with alcohols and thiols to give three addition products, **7**, **8**, and **9**. Phenylhydrazone (**3**), semicarbazone (**4**), hydrazone (**5**), and azine (**6**) of hexafluoroacetone were also obtained directly from **1** and the corresponding carbonyl reagents.

Hexafluoroisopropylideneimine (**2**, R=H) and its-*N*-substituted derivatives appear to be useful intermediates for the syntheses of hexafluoroisopropyl compounds. Although Middleton *et al.*[1,2] have prepared the imine and its *N*-methyl derivative by the reaction of hexafluoroacetone with either ammonia or methylamine, followed by the dehydration of the resulting adducts, the present knowledge of the experimental conditions for the preferential elimination of water from adducts of hexafluoroacetone with other amines is far from satisfactory.

On the other hand, Zeifman *et al.*[3] prepared *N*-phenylhexafluoroisopropylideneimine (**2**, R=Ph) by a Wittig-like reaction, which involved the reaction of hexafluoroacetone with phenylisocyanate in the presence of triphenylphosphine oxide as the catalyst. Furthermore, they prepared the oxime and semicarbazone of hexafluoroacetone by the elimination of aniline from the corresponding adducts obtained from the condensation of *N*-phenylhexafluoroisopropylideneimine with hydroxylamine[4] and semicarbazide[5] respectively.

In the course of our investigation of the organic fluorine sulfur compounds, it was necessary to study the reactivity of fluoroalkylthiocarbonyl compounds. Hexafluorothioacetone is known as an unstable gas which dimerizes very readily into a stable liquid, 2,2,4,4-tetrakis(trifluoromethyl)-1,3-dithiethane (**1**).[6] Our studies of the nucleophilic reactions of this dimer have revealed that aryl- and alkylamines gave *N*-substituted hexafluoroisopropylideneimines easily, and that it is a convenient general method for the preparation of the imines of this type. Carbonyl reagents also gave the phenylhydrazone and semicarbazone of hexafluoroacetone directly.

We also carried out several nucleophilic addition reactions across the C=N– double bonds of these imines; we could thus obtain 2-alkoxy- and 2-alkylthio-2-arylaminohexafluoropropanes.

Results and Discussion

The Preparation of N-*Substituted Hexafluoroisopropylideneimines.* The dimer of hexafluorothioacetone (**1**) (bp 110 °C) can be prepared directly from hexafluoropropene and sulfur in sulfolan in the presence of potassium fluoride.[7] This compound is reported to be very

1) W. J. Middleton and C. G. Krespan, *J. Org. Chem.*, **30**, 1398 (1965).
2) W. J. Middleton, U. S. 3226439 (1965).
3) Yu. V. Zeifman, N. P. Gambaryan, and I. L. Knunyants, *Dokl. Akad. Nauk SSSR*, **153**, 1334 (1964).
4) Yu. V. Zeifman, N. P. Gambaryan, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, **1965**, (3), 450.
5) Yu. V. Zeifman, N. P. Gambaryan, and I. L. Knunyants, *Zh. Vses Khim. Obshch. im D. I. Mendeleeva*, **10**(2), 235 (1965).
6) W. J. Middleton, E. G. Howard, and W. H. Sharkey, *J. Org. Chem.*, **30**, 1375 (1965).
7) I. L. Knunyants, *Dokl. Akad. Nauk*, **183**, 598 (1968).

Table 1. Preparation of 2, 4, and 5

$(CF_3)_2C=N-R$

	Compound R	Yield %	Bp (°C/mmHg) [mp (°C)]	IR (cm^{-1}) (C=N)	^{19}F NMR[a] *syn*	^{19}F NMR[a] *anti*	F Anal (%) Found	F Anal (%) Calcd
2	Ph	67	75/91	1680	−8.6	−16.2	47.9	47.3
	o-MeC_6H_4	78	72—73/53	1698	−8.4	−15.0	44.7	44.7
	m-MeC_6H_4	70	83—84/71	1604	−8.4	−16.4	45.3	44.7
	p-MeC_6H_4	69	85—86/53	1660	−8.4	−16.1	45.2	44.7
	2,4-$Me_2C_6H_3$	45	70—71/34	1612	−8.7	−15.7	42.0	42.3
	m-FC_6H_4	71	75—78/97	1618	−8.2	−16.2	51.6	51.3
	p-FC_6H_4	65	118—120/108	1640	−8.1	−14.7	50.9	51.3
	m-$CF_3C_6H_4$	59	80—83/48	1620	−8.0	−16.0	55.0	55.3
	m-*i*-$C_3F_7C_6H_4$	73	90—92/58	1605	−8.1	−16.0	60.9	60.4
	p-*i*-$C_3F_7C_6H_4$	76	78—81/38	1603	−6.4	−16.8	61.2	60.4
	o-ClC_6H_4	49	75/25	1594	−9.1	−15.1	40.9	41.4
	m-ClC_6H_4	78	71—72/21	1595	−8.4	−16.2	41.7	41.4
	p-ClC_6H_4	39	65—66/21	1592	−8.7	−16.1	41.1	41.4
	o-$MeOC_6H_4$	50	95—96/43	1604	−9.2	−12.7	42.7	42.0
	p-$MeOC_6H_4$	13	76—77/15	1664	−9.1	−15.4	42.5	42.0
	n-C_3H_7	18	52—53	1691	−7.4	−13.6	55.5	55.0
	n-C_5H_9	20	63—64	1634	−7.2	−14.7	51.1	51.5
3	NHPh	66	91—92/23	1664	−8.7	−15.8	44.8	44.5
4	$NHCONH_2$	90	[131—132]	1640	−11.3	−12.9	50.7	50.9
5	NH_2	43	93—96	1600	−12.0[b]	−13.4[b]	62.7	63.3

a) δ ppm from ext. CF_3CO_2H in CCl_4.
b) lit,[1] −11.5, −12.8.

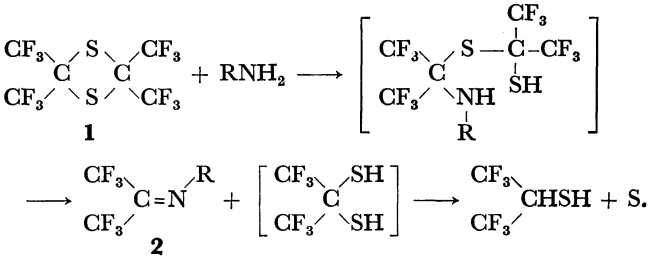
susceptible to bases and reacts with sodium methoxide in methanol rapidly to give a fluorine-free compound, dimethyl α-methylthio-α-methoxymalonate, in a poor yield.[6] However, no other nucleophilic reaction of this dimer has appeared in the literature. We carried out several reactions of the dimer with amines under more moderate conditions, and found that both aryl- and alkylamines reacted with the dimer at room temperature, with a liberation of sulfur.

For example, when the dimer was allowed to react with 2 mol of *p*-toluidine in dimethylformamide, an oily material was obtained. Among the various solvents examined, such as alcohol, acetonitrile, dioxane, and other polar solvents, dimethylformamide was the most effective in promoting the reaction.

The product was sulfur-free, but it still contained trifluoromethyl groups. The structure of this compound was elucidated by a study of the IR, ^1H and ^{19}F NMR, and mass spectra to be *N*-*p*-tolylhexafluoroisopropylideneimine (**2** R=$C_6H_4CH_3$). In the IR spectrum, the presence of the C=N group was shown by the band at 1660 cm^{-1}, and in the ^{19}F NMR spectrum, two singlet peaks, −8.4 and −16.1 ppm from ext. CF_3COOH in CCl_4, appeared, corresponding to *syn*- and *anti*-CF_3 respectively.[8-10] In the mass spectrum, the parent peak, M^+ 255, and other fragment peaks, such as *m/e* 186 ($C_9H_7NF_3$), 91 (C_7H_7), and 69 (CF_3), appeared appropriately.

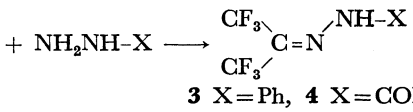
The other *N*-aryl hexafluoroisopropylideneimines were prepared similarly by using aniline and its substituted derivatives. Such alkylamines as *n*-propyl- and *n*-butylamine gave *N*-alkylimines, but in poorer yields. (Table 1).

Considering the yields of the products and the amount of sulfur liberated during the reaction, the reaction seemed to proceed according to the following scheme:



Many attempts to capture bis(trifluoromethyl)methanethiol in the reaction mixtures were unsuccessful, probably because of the extreme instability of this compound.

In addition to aryl- and alkylamines, phenylhydrazine and semicarbazide also attacked the dimer in dimethylformamide at room temperature; phenylhydrazone and semicarbazone of hexafluoroacetone were thus obtained.



3 X=Ph, **4** X=$CONH_2$

When unsubstituted hydrazine was used as nucleophile, the reaction in dimethylformamide was too vigorous and gave only a tarry material. In a milder solvent, such as acetonitrile, the reaction proceeded smoothly and hexafluoroacetone hydrazone (**5**) and

8) J. K. Ruff, *J. Org. Chem.*, **32**, 1675 (1967).
9) G. E. Hall, W. J. Middleton, and J. D. Roberts, *J. Amer. Chem. Soc.*, **93**, 4778 (1971).
10) F. J. Weigert, *J. Org. Chem.*, **37**, 1314 (1972).

Table 2. Preparation of **7** and **8**

$$X\text{–}C(CF_3)_2\text{–}NH\text{–}Ar$$

Compound X	Compound Ar	Yield %	Bp °C/mmHg	IR (cm^{-1}) N–H	^{19}F NMR (ppm)	F Anal (%) Found	F Anal (%) Calcd
MeO	Ph	34	85/25	3306	−3.8	41.6	41.7
	o-MeC_6H_4	35	88—89/18	3360	−4.9	39.8	39.7
	m-MeC_6H_4	28	99—100/26	3332	−3.5	39.1	39.7
	p-MeC_6H_4	33	96—97/26	3358	−3.6	40.1	39.7
	2,4-$Me_2C_6H_3$	28	105/21	3343	2.0	38.0	37.8
	o-ClC_6H_4	38	98/27	3386	−4.8	37.5	37.1
	m-ClC_6H_4	51	118/28	3360	−3.5	37.6	37.1
	p-ClC_6H_4	20	106/19	3410	−3.8	37.3	37.1
	o-$MeOC_6H_4$	35	107/21	3398	1.9	38.0	37.6
EtO	Ph	28	84/24	3342	−5.2	40.0	39.8
	o-MeC_6H_4	31	93/24	3358	−3.5	37.5	37.8
	m-MeC_6H_4	42	98/26	3359	−5.2	37.5	37.8
	p-MeC_6H_4	29	96—98/24	3343	−5.1	38.6	37.8
	2,4-$Me_2C_6H_3$	26	100/24	3305	−2.8	36.9	36.2
	o-ClC_6H_4	23	96/24	3391	−2.1	35.6	35.4
	m-ClC_6H_4	33	105—106/24	3353	2.0	35.1	35.4
EtS	Ph	27	84/31	3286	−4.3	37.9	37.6
	o-MeC_6H_4	30	88/22	3303	−4.3	35.6	35.9
	m-MeC_6H_4	61	133/25	3401	−7.3	36.1	35.9
	p-MeC_6H_4	35	101—104/24	3328	−7.3	36.2	35.9
	2,4-$Me_2C_6H_3$	30	83/20	3316	−4.0	34.6	34.4
	o-ClC_6H_4	54	88/25	3321	−4.3	34.1	33.9
	m-ClC_6H_4	21	106/27	3318	−4.1	33.5	33.9

a) δ ppm from ext. CF_3CO_2H in CCl_4.

azine (**6**) were obtained in yields of 43 and 11% respectively.

$$\mathbf{1} + NH_2NH_2 \longrightarrow \underset{\mathbf{5}}{(CF_3)_2C{=}N{-}NH_2} + \underset{\mathbf{6}}{(CF_3)_2C{=}N{-}N{=}C(CF_3)_2}$$

Thus, the hydrazones of hexafluoroacetone were prepared directly from the hexafluorothioacetone dimer and the corresponding carbonyl agents; this seemed to be a convenient preparative route because several steps had previously been required for the preparation of these compounds.[5]

Hexafluoroisopropylideneimines are also susceptible to nucleophiles. Zeifman *et al.*[3,4] reported several reactions of the imines, especially reactions with amines, by which an exchange of imino groups occurred. We examined the addition of alcohols and thiols across the C=N– double bond of *N*-arylhexafluoroisopropylideneimines and prepared a number of 2-alkoxy- and 2-alkylthio-2-arylaminohexafluoropropanes, **7** and **8**, for pharmacological purposes.

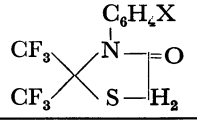
Methyl and ethyl alcohols reacted with the imines by means of refluxing in the presence of a small amount of alkali, while ethanethiol reacted under a nitrogen atmosphere at room temperature. The structures of the products were evident from the IR and the ^1H and ^{19}F NMR spectra, as well as, from fluorine analysis. In each compound, only one singlet signal appeared in the ^{19}F NMR, and the presence of N–H was shown in the IR spectrum (Table 2).

$$(CF_3)_2C{=}N{-}Ar + R\text{–}ZH \longrightarrow R\text{–}Z\text{–}C(CF_3)_2\text{–}NH\text{–}Ar$$

7 Z=O, **8** Z=S

It is known that the reaction between the Schiff bases and thioglycolic acid gives 4-thiazolidinones, and that their derivatives are sometimes useful as drugs.[11,12]

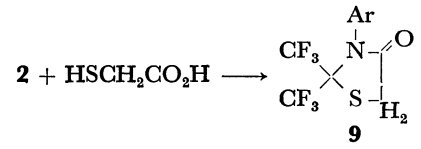
Table 3. Preparation of **9**



Compound X	Yield %	Mp °C	IR (cm^{-1}) C=O	F Anal (%) Found	F Anal (%) Calcd
H	85	97—98	1702	36.1	36.2
p-Me	81	119.5—120	1704	34.8	34.7
m-F	50	105—106	1710	39.3	39.9
p-F	56	108—109	1710	39.4	39.9
m-CF_3	60	101—102	1709	44.8	44.6
m-*i*-C_3F_7	46	97—98.5	1710	50.8	51.1
p-*i*-C_3F_7	52	101—102	1710	51.3	51.1
m-Cl	60	91.5—92	1705	33.0	32.6
p-Cl	58	102—102.5	1708	32.8	32.6

11) A. R. Surrey, *J. Amer. Chem. Soc.*, **69**, 2911 (1947).
12) H. D. Troutman and L. M. Long, *ibid.*, **70**, 3436 (1948).

We have also prepared 3-aryl-4-thiazolidinones (**9**), which carry geminal trifluoromethyl groups at the 2-position, by the reaction of *N*-arylhexafluoroisopropylideneimines with thioglycolic acid (Table 3).



9

Experimental

Hexafluorothioacetone Dimer (1). This compound was prepared according to the method of Knunyants.[7] Bp 109—110 °C; yield, 74% (lit, bp 110—111 °C, yield, 72%).

N-*Arylhexafluoroisopropylideneimines (2).* These compounds were prepared in a similar manner; one example will be described below.

To a stirred mixture of *p*-toluidine (4.3 g, 0.04 mol) and dimethylformamide (40 ml), **1** (7.3 g, 0.02 mol) was added, drop by drop, at room temperature; stirring was then continued for 4 hr at that temperature. The liberated sulfur (0.43 g, 0.013 mol) was removed by filtration, and the filtrate was poured into water. The separated oily material was extracted with diethyl ether, and the extract was dried over magnesium sulfate. After removing the solvent, the residual oil was subjected to vacuum distillation. *N-p*-Tolylhexafluoroisopropylideneimine (**2**, R=*p*-$CH_3C_6H_4$) (3.5 g) (bp 85—86 °C/53 mmHg) was thus obtained in a yield of 35%. IR: 1660 (C=N), 1300, 1218 (C–F) cm^{-1}. NMR (in CCl_4): τ 7.69 (CH_3, s), 2.86—3.38 (arom-H).

Hexafluoroacetone Phenylhydrazone (3). Phenylhydrazine (2.5 g, 0.044 mol), **1** (8.0 g, 0.022 mol), and dimethylformamide (40 ml) were used as in the preceding reaction, and worked up similarly. A fraction with a bp of 91—92 °C/23 mmHg was collected to give **3** (3.7 g, 66%).

Hexafluoroacetone semicarbazone (**4**) was prepared in a similar manner.

Hexafluoroacetone Hydrazone (5) and Azine (6). Anhydrous hydrazine (9.6 g, 0.3 mol) was added, drop by drop, to a solution of **1** (36.4 g, 0.1 mol) in acetonitrile (80 ml), after which the mixture was stirred for 1.5 hr at room temperature. After removing the liberated sulfur by filtration, the filtrate was poured into water and worked up as usual. Two products were obtained by fractional distillation: azine, **6** (3.6 g, 11%) (bp 67—70 °C (lit,[1] bp 67—67.5 °C)) and hydrazone, **5** (15.4 g, 43%) (bp 93—96 °C (lit,[1] bp 95.5—96 °C)).

2-Alkoxy-2-arylaminohexafluoropropanes (7). An example will be given below.

A mixture of *N*-phenylhexafluoroisopropylideneimine (**2**, R=Ph) (3.7 g, 0.015 mol), methanol (6.4 g, 0.19 mol), and potassium hydroxide (1.0 g, 0.015 mol) was refluxed for 5 hr. The usual work-up process gave a product (**7**, R=Me, Ar=Ph), 1.4 g (34%) (bp 85 °C/25 mmHg). IR (KBr): 3306 (N=H), 1258, 1211, 1178 (C–F) cm^{-1}. NMR (in CCl_4): τ 5.50 (OMe), 2.55—3.27 (arom. and NH).

2-Ethylthio-2-arylaminohexafluoropropanes (8). Under a nitrogen atmosphere, a mixture of **2**, R=Ph (2.6 g, 0.011 mol), ethanthiol (0.8 g, 0.013 mol), and potassium hydroxide (0.8 g, 0.012 mol) was stirred for 5 hr at room temperature. The usual work-up process gave **8**, R=Et, Ar=Ph (0.9 g, 27%); bp 84 °C/31 mmHg. IR (KBr): 3286 (N–H), 1257, 1217 (C–F) cm^{-1}. NMR (in CCl_4): τ 7.30 (CH_2, q), 8.80 (CH_3, t), 2.12 (NH, broad), 2.79—3.32 (arom.).

2,2-Bis(trifluoromethyl)-3-aryl-4-thiazolidinones (9). A mixture of *N*-phenylhexafluoroisopropylideneimine (5.68 g), thioglycolic acid (6.0 g), triethylamine (0.5 g), and dried benzene (30 ml) was refluxed under a nitrogen atmosphere for 48 hr, and then the benzene was removed by distillation. The residue solidified on cooling; it was recrystallized from *n*-hexane to give **9**, Ar=Ph (6.3 g, 85%) (mp 97—99 °C). Other *N*-aryl compounds were prepared in a similar manner.