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ALKYLATION REACTIONS OF PENTAFLUOROTHIOPHENOL IN DIMETHYLFORMAMIDE.

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The alkylation of thiols with alkyl halides is usually accomplished in the presence of a strong base e.g. NaOH, t-amines etc. in order to promote the nucleophilicity of the sulphur atom and to remove the halide ion as it is released. In the reaction of thiophenol with aryl halides it has been found that the yields are highest when the metal ion is potassium and the solvent, dimethylformamide[1], a medium of proven success for aromatic nucleophilic substitution reactions[2,3,4].

In the case of pentafluorothiophenol the presence of an inorganic,[5,6] or even weak organic, base[7] causes extensive polymerisation to an intractable product as a result of the repeated nucleophilic substitution of the p-fluorine atoms by the thiolate anion. Alkylation or arylation of pentafluorothiophenol therefore poses problems and in the preparation of methyl pentafluorophenyl sulphide, the dangerous reagent diazomethane has been employed[5,6].

During a study of the reaction of thioureas with perfluoroaromatic compounds[7] it was observed that pentafluorothiophenol was polymerised upon addition to dimethylformamide and it seemed likely that facile alkylation of the thiophenol by reactive alkyl halides might be brought about in a competitive reaction without the necessity of adding a strong base. Indeed, one instance of such a reaction has been reported[10] in which pentafluoronitrobenzene was reacted in dimethylformamide with pentafluorothiophenol to give 4-nitro-tetrafluorophenyl (pentafluorophenyl) sulphide in high yield, although a general examination does not appear to have been carried out.

In the present work pentafluorothiophenol was added to solutions of a series of alkyl or aryl halides in dimethylformamide and it was found that the reaction took different courses, depending on the reactivity of the halide, as generalised in the following equations.

$$(1) \qquad Ph_f\,SH + RX \xrightarrow[25°/20\ hr.]{DMF} Ph_f\,SR + HX$$

$$[R = \text{Alkyl or activated aryl},\ X = \text{halogen}]$$

$$(2) \qquad n\ Ph_f\,SH + RX \xrightarrow[24°/20\ hr.]{DMF} Ph_f\,S\left[Ph_f\,S\right]_{n-1} R + n\,HX$$

$$[R \text{ and } X \text{ as above},\ n > 0]$$

Thus the polymerisation of pentafluorothiophenol is represented by eq. (2) where RX is omitted. When RX was a simple alkyl chloride (R = propyl, butyl or hexyl) the only reaction observed was the complete polymerisation of the pentafluorothiophenol, but when more reactive compounds (e.g. benzyl chloride) were used, two products having identical N.M.R. spectra, could be obtained in accordance with equations (1) and (2) above, depending on the nature of the halogen atom as indicated in the table of reaction products. It also seemed worthwhile to examine the possibility of using a multifunctional halide in order to see if repeated substitution at the same carbon atom was possible. Iodoform was chosen, and reactions of types (1) and (2) occurred to afford tris (pentafluorophenylthio) methane (I) and a higher molecular weight material (II) which appeared to have resulted from further reactions of pentafluorothiophenol at the para positions of the former product.

$$Ph_f\,SH + CHI_3 \xrightarrow[25°/20\ hr.]{DMF} \underset{I}{\left(Ph_f\,S\right)_3 CH} + \underset{II}{Ph_f\,S\left[Ph_f\,S\right]_n CH\left(S\,Ph_f\right)_2}$$

The value of n in II was not determined and it was not possible to tell if further substitution had occurred in the same chain (as formally indicated in II) or in more than one chain.

Aromatic compounds containing activated fluorine atoms (e.g. octafluorotoluene) also combined readily with pentafluorothiophenol but relatively non-activated compounds (e.g. iodobenzene) failed to react.

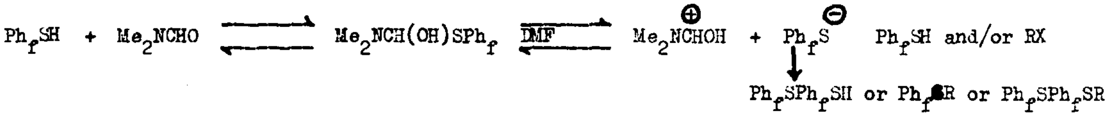
In most cases of thiol alkylation bases, organic or inorganic, are usually needed in order to generate the powerfully nucleophilic thiolate anions. In the present work it is difficult to see why such anions should be formed directly in view of the virtually non basic character of dimethyl formamide[8,9]. On the other hand the ready solubility of halogen acids[4] and the formation of stable, distillable derivatives[11] may shed some light on the behaviour in this solvent.

The possibility that amines might be formed <u>in situ</u> by the decomposition of dimethylformamide by alkyl halides[12] can be discounted because

a) The formation of amines in this type of process and under the present mild conditions is very slow[12].

b) The alkyl halide appears to be used up in reactions with pentafluorothiophenol.

Under the reaction conditions used, thiophenol itself is unreactive and so, presumably, the enhanced acidity of the fluorinated thiophenols is important. If this is the case then a mechanism involving an initial reaction of the thiol with the solvent may be operative, according to the scheme below



$$\mathrm{Ph_fSH + Me_2NCHO \rightleftharpoons Me_2NCH(OH)SPh_f \overset{DMF}{\rightleftharpoons} Me_2N\overset{\oplus}{C}HOH + Ph_fS^{\ominus} \quad Ph_fSH\ and/or\ RX}$$

$$\mathrm{Ph_fS^{\ominus} \downarrow Ph_fSPh_fSH\ or\ Ph_fSR\ or\ Ph_fSPh_fSR}$$

In such a process dimethyl formamide would not react as a base in the usually accepted manner although the overall effect might be the same. The carbonium ion formed in the second equilibrium could be resonance stabilised, making the process more likely and the formation of deep yellow-orange colours (destroyed on addition to water) may be indicative that reactions of this type are taking place although, obviously, further work is necessary in order to elucidate these interesting possibilities.

The products were isolated by pouring the reaction mixtures into cold water followed either by filtration or ether extraction and distillation. The table illustrates the physical data of the compounds prepared in the reactions described and in all cases Mass Spectroscopic molecular weights, N.M.R., I.R. and elemental analyses were in excellent agreement with the theoretical requirements.

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REACTION PRODUCTS FROM PERFLUOROTHIOPHENOL AND ORGANIC HALIDES IN DMF.

Perfluorothiophenol	Halide	Products	Cryst. from	m.p.(°C)	b.p./mm.	Yield (%)*
Ph_fSH	Simple RCl	Polymer	—	>300 (dec.)	-	100
"	$PhCH_2Cl$	Ph_fSCH_2Ph	MeOH	40-41	96/0.3	33
"		$Ph_fS\ Ph_fS\ CH_2Ph$	MeOH	79-80	160/0.3	66
"	2:4 $(NO_2)_2PhCl$	2:4$(NO_2)_2PhSPh_f$	EtOH	173-174	-	98
"	[illegible]:4 (NO_2) PhCl	Polymer	—	>300 (dec.)	-	100
"	EtBr	Polymer	—	>300 (dec.)	-	5
	"	$Ph_f\ S\ Ph_f\ S\ Et$	$EtOH/H_2O$	35-36	120/0.3	80
"	$BrCH_2\ COOEt$	Ph_fSCH_2COOEt	—	-	85-90/0.2	93
"	Me I	Ph_fSMe	—	-	167-170/760	93
"	Et I	Ph_fSEt	—	-	64-66/9	84
"	Bu I	Ph_fSBu	—	-	94/9	76
"	CH I_3	CHI_3 (35% recovered)	$EtOH/H_2O$	118-119	-	-
		$(Ph_fS)_3CH$	EtOH	134-135	-	25
		$^{**}Ph_fS(Ph_fS)_nCH(SPh_f)_2$	Bz/petrol	198-200	-	35
"	Ph I	Polymer	—	-	-	100
	$CF_3\ Ph_f$	$4\text{-}CF_3Ph_fSPh_f$	$EtOH/H_2O$	49-50		82
$4\text{-}CF_3Ph_fSH$	$CF_3\ Ph_f$	$4,4'\text{-}CF_3Ph_fSPh_fCF_3$	EtOH	71-72		92

* Based on the perfluorothiophenol

** A generalised structure only and not confirmed