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PERFLUOROALKYL AND PERFLUOROALKYLETHER CHLOROSULFATES IN THE SYNTHESIS OF SUBSTITUTED BENZAZOLES

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SUMMARY

Perfluoroalkyl and perfluoroalkylether chlorosulfates prepared from corresponding iodides have been utilized in the synthesis of 2-substituted benzoxazoles, benzothiazoles and benzimidazoles. The chlorosulfates react readily with the appropriate 2-hydroxy, 2-mercapto and 2-aminoanilines at or below ambient temperatures. The products are a mixture of the heterocyclic compounds and their precursor anilides except in the case of 2-hydroxyaniline, which gives only the anilide. The initial products obtained are readily converted to the heterocyclic compounds in fair to high yields.

INTRODUCTION

A number of methods are available for the synthesis of 2-(perfluoroalkyl)- and 2-(perfluoroalkylether) benzoxazoles, benzothiazoles and benzimidazoles [1-5], most of them being analogous to well-established methods in hydrocarbon chemistry. In general, reactions of appropriate aliphatic carboxylic acids and their derivatives with ortho-substituted aromatic amines are utilized in preparing these heterocycles.

Fluoroalkylchlorosulfates are currently under investigation in this Laboratory. These compounds are known to react readily with ammmonia to yield amides in nearly quantitative yield [6]. We have extended this reaction to ortho-substituted anilines to obtain heterocyclic compounds with perfluorinated substituents.

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This procedure offers yet another method of preparing these heterocycles or their precursors at relatively mild conditions, and is particularly suitable when the available fluorinated reagent is a perfluoroalkyl or perfluoroalkylether iodide rather than a carboxylic acid.

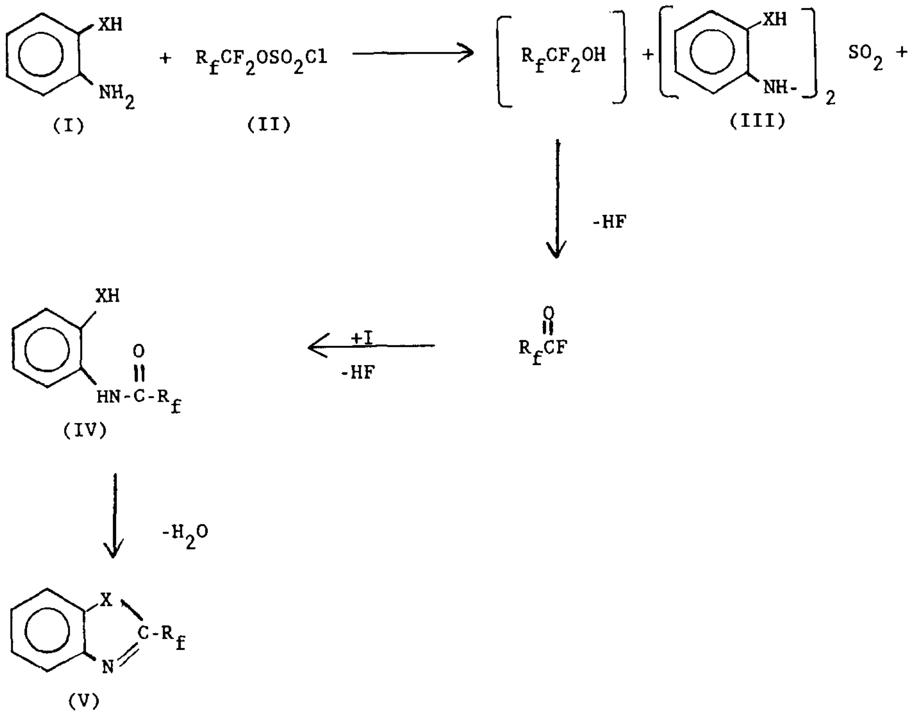
RESULTS AND DISCUSSION

Excess ortho-substituted anilines were used in all reactions with chlorosulfates. Considering the mechanism proposed by Hauptschein et al. [6] for the conversion of a chlorosulfate to an acid amide, the reaction in general leading to the formation of benzazoles is represented as in Scheme 1.

Since acid fluorides are intermediates in this process, these reactions of chlorosulfates were similar to the acylations of ortho-substituted anilines with acid fluorides [2,5].

The reactions were carried out by slow addition of the chlorosulfates (II) to the substituted anilines in anhydrous diethylether at approximately 5°C. The chlorosulfates reacted completely on addition as determined by gas chromatographic analysis of the reaction mixtures. Amine salts, apparently a mixture of hydrochloride and hydrofluoride precipitated on addition. In the case of o-phenylenediamine (Ia) the reaction mixture developed a deep black color; and therefore, considering the possibility of decomposition, reaction of Ia with IIn was repeated at -70°C. The yield and the nature of the reaction were however not significantly different from those of the reaction at 5°C.

In reactions of Ia and Ic, the products were essentially a mixture of ortho-substituted anilides (IV), and the benzazoles (V) formed by dehydrative cyclization of IV. In these cases, it was difficult to obtain an accurate estimate of the product composition as the anilides were being slowly converted into the heterocycles in the reaction medium. Stirring the reaction mixture at ambient temperature for 3-4 days resulted in complete conversion of the anilides to the heterocyclic compounds Va and Vc. However, it was more convenient to isolate the crude products and heat the crude products to



Ia; X = NH
b; X = O
c; X = S
IIm; R_f = n-C_7F_{15}-
n; R_f = $(CF_3)_2CFO(CF_2)_5$-

IVa, Va; X = NH
b, b; X = O } R_f = n-C_7F_{15}-
c, c; X = S

IVd, Vd; X = NH
e, e; X = O } R_f = $(CF_3)_2CFO(CF_2)_5$-
f, f; X = S

SCHEME 1.

effect cyclization in a much shorter time period. Reaction of Ib gave only the substituted anilides (IVb and IVe) which did not eliminate water during reaction with chlorosulfates. It was necessary to isolate the 2-hydroxyanilides and treat them with polyphosphoric acid at about 200°C to affect dehydrative cyclization.

No attempt was made to identify all the side products that are formed. Thus the sulfanilides (III) were not detected. This may be due to the lack of volatility of these compounds, and the fact that routine analysis of reaction mixtures were carried out mainly by GC/MS. In reactions of Ic, acylated disulfides could be identified by GC/MS while unacylated disulfide could be separated from the reaction mixture based on its limited solubility in diethylether. These disulfides are apparently formed during work-up of the reaction mixture, by atmospheric oxidation of thiols. In reactions of Ia, trace amounts of ortho-disubstituted anilide, $C_6H_4[NHC(O)R_f]_2$, could be identified by GC/MS. Use of large excess of Ia apparently inhibited the formation of this dianilide.

EXPERIMENTAL

Most of the starting materials were obtained from commercial sources and were used without further purification except 2-aminobenzenethiol which was distilled and stored under nitrogen before use. The iodide $(CF_3)_2CFO(CF_2)_6I$ was received as a gift from Allied Chemical Company. The new compounds isolated were characterized by IR, MS and combustion analysis. All melting and boiling points are uncorrected. IR spectra were obtained on a Perkin-Elmer Model 600 Infrared Spectrophotometer, using KBr wafers for solids and capillary film (neat) for liquids. Gas chromatographic analyses were performed on Perkin-Elmer Sigma 1 or Sigma 2B instrument using 2' x 1/4" stainless steel column packed with 5% Dexsil 400 on 100/120 Supelcoport or 12' x 1/4" column packed with 10% SE-30 on 80/100 Supelcoport. Mass spectra were determined by electron impact on a Finnigan 4021 Mass spectrometer. All reactions were carried out under an atmosphere of dry nitrogen. The yields, physical properties and relevent analytical data of the compounds synthesized are reported in Table 1.

Preparation of $R_fCF_2OSO_2Cl$ [IIm (nc) and IIn (nc)]

A mixture of R_fCF_2I (0.33 mol) and chlorosulfonic acid (2.61 mol) was heated to reflux (~ 130°C) under dry N_2. After 4 h, the reaction mixture was allowed to cool to room temperature. The bottom layer was separated, washed with water (3 x 100 ml) limiting the contact time to a few minutes and was dried over anhydrous magnesium sulfate. Pure samples of the chlorosulfates were obtained as colorless liquids by distillation and were stored under N_2. Both the compounds, IIm and IIn showed IR absorption bands (asym. SO_2 stretch) at 1447 and 1460 cm^{-1}, respectively.

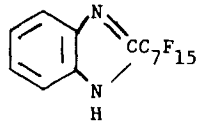
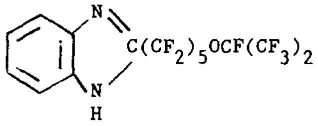
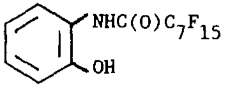
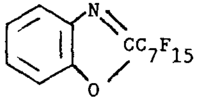
Preparation of the benzimidazole, Vd (nc)

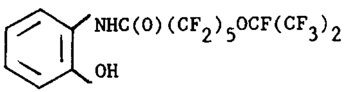
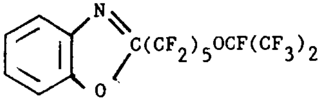
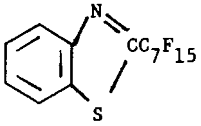
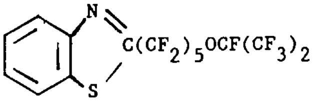
To o-phenylenediamine (Ia) (2.16 g, 20.0 mmol) in diethylether (20 ml), cooled to ~ 5°C in an ice-bath was added, IIn (2.0 g, 3.3 mmol) during 5 min. An exotherm was observed, and the reaction mixture assumed an intense black color. The reaction mixture was stirred at ~5°C for 30 min. The precipitated amine salts were filtered off, and the solvent and any low-boiling by-products were removed on a rotary vacuum evaporator. The remaining brown solid was washed with water (3 x 20 ml) and petroleum ether (3 x 20 ml). The crude product obtained was sublimed at 170°C/80 mm to obtain the pure benzimidazole (Vd) as a white solid (1.6 g, yield 87%).

The reaction was repeated at -70°C using the same ratio of reactants. On addition of the chlorosulfate an intense black color developed. The contents were stirred at -70°C for 1 h and was processed as before. The yield of the product was similar to that obtained for the reaction at 5°C. The IR spectrum of the compound showed the following absorptions: ~ 3100 (broad, s), ν (N-H, bonded); 1678 (m), 1593 (w), 1533 (w), 1497 (m), 1440 (s), ring stretch; and 1400-1000 cm^{-1} (s), ν (C-F).

TABLE 1

Characterization of Compounds Synthesized

COMPOUND	Isolated Yield (%)	m.p. [b.p.] (°C)	M.S.[a]	COMBUSTION DATA (Calculated/Found)		
				C	H	N
n-$C_8F_{17}OSO_2Cl$ (IIm)	61	[78/10 mm]	419 $(M\text{-}OSO_2Cl)^+$	17.97[b] 17.69	0 0.02	-
$(CF_3)_2CFO(CF_2)_6OSO_2Cl$ (IIn)	58	[88/10 mm]	485 $(M\text{-}OSO_2Cl)^+$	18.00[c] 18.05	0 0.05	-
 (Va)	77	199	486 (M^+)	34.59 34.32	1.04 1.06	5.76 5.67
 (Vd)	87	166	552 (M^+)	32.63 32.55	0.93 1.00	5.07 5.09
 (IVb)	88	129 {lit. [7] 136.5-7.5}	505 (M^+)	33.28 33.26	1.20 1.34	2.77 2.86
 (Vb)	74	[80/0.18 mm] (lit. [7] 133-4/20 mm)	487 (M^+)	34.51 34.68	0.83 0.81	2.88 2.81

 (IVe)	80	121	571 (M^+)	31.54 31.40	1.06 1.15	2.45 2.49
 (Ve)	60	[59/0.05 mm]	553 (M^+)	32.57 32.32	0.73 0.80	2.53 2.48
 (Vc)	68	69 (lit. [8] 63-5)	503 (M^+)	33.40 32.92	0.80 0.92	2.78 2.97
 (Vf)	67	46	569 (M^+)	31.63 31.80	0.70 0.95	2.46 2.44

[a] Determined by electron impact. [b] Cl: 6.63/6.68; S: 6.00/6.29. [c] Cl: 5.90/5.67; S: 5.34/5.63.

Preparation of Va (nc)

2-(Perfluoro-n-heptyl) benzimidazole (Va) was prepared in 77% yield using identical procedure used for the preparation of Vd. IR: ~ 3100 (broad, s), ν (N-H, bonded); 1692 (w), 1598 (w), 1523 (m), 1494 (m), 1440 (s), ring stretch; and 1400-1000 cm^{-1} (s), ν (C-F).

Preparation of the 2-hydroxyanilide, IVe (nc) and benzoxazole, Ve (nc)

To a solution of 2-aminophenol (Ib) (4.36 g, 40.0 mmol) dissolved in diethylether (50 ml), cooled to ~ 5°C was added IIn (4.0 g, 6.7 mmol) during 10 min. There was an exotherm raising the temperature to ~ 10°C, and the reaction mixture turned dark. The contents were stirred for 2 h while allowing the flask to warm up to room temperature. The amine salts precipitated were filtered off, the dark brown solution was washed with water (3 x 30 ml) and dried over anhydrous $MgSO_4$. The solvent and any low-boiling products were removed on a rotary vacuum evaporator at 40°C. The crude product was obtained as a brown solid. Recrystallization from diethylether-hexane yielded 3.05 g of IVe (yield 80%). IR: 3380 (m) and 3312 (m), ν (N-H) and ν (O-H); ~ 3060 (vw), ν (Ar-H); 1702 (s), ν (C=O); 1551 (m); and 1400-1000 cm^{-1} (s), ν (C-F).

For the conversion of the hydroxyanilide to benzoxazole, compound IVe (3.7 g) was heated under dry N_2 with polyphosphoric acid (~ 3 g) at about 200°C for a period of 2 h with efficient stirring. Distillation of the black mixture yielded 2.2 g of Ve. Yield 60% b.p. 59°C/0.05 mm. IR: 3080 (vw), ν (Ar-H); 1788 (m), 1618 (m), 1573 (m), 1480 (w), 1451 (m), ring stretch; and 1400-1000 cm^{-1} (s), ν (C-F).

Preparation of IVb and Vb [7]

These compounds were prepared in the same manner as IVe and Ve. The IR spectrum of IVb showed the following absorptions: 3380 (m) and 3312 (m), ν (N-H) and ν (O-H); 3040 (vw), ν (Ar-H); 1700 (s) and 1690 (s), ν (C=O); 1550 (m); and 1400-1000 cm^{-1} (s), ν (C-F).

The compound Vb was obtained as a colorless liquid. IR: 3080 (vw), ν (Ar-H); 1787 (w), 1617 (m), 1572 (m), 1478 (w), 1450 (m), ring stretch; and 1400-1000 cm^{-1} (s), ν (C-F).

Preparation of the benzothiazole, Vf (nc)

To a solution of 2-aminobenzenethiol (Ic) (3.5 g, 28.0 mmol) in diethylether (25 ml), cooled to ~5°C was added IIn (4.2 g, 7.0 mmol) during 20 min. A mild exotherm was observed, but the temperature was maintained below 10°C. The reaction mixture slowly turned brown depositing solids. The contents were stirred for 2 h at ~ 5°C. The reaction mixture was allowed to warm up to room temperature and stirred at room temperature overnight (18 h). After the reaction, the contents were filtered to separate the solids. The solid was treated with water to dissolve the amine salts. A water-insoluble solid was obtained (0.8 g) which was identified as 2,2'-diaminodiphenyldisulfide. The ether layer was treated with 2N•HCl, washed with water, dried over anhydrous $MgSO_4$ and stripped to obtain 3.6 g of a yellow solid. This product melted at a broad range of 40-90°C. Its IR spectrum showed absorptions at 3360 (m), ν (N-H); 3070 (vw), ν (Ar-H); 2640 (vw), ν (S-H); 1735 (s), ν (C=O); 1650 (m), 1585 (m), 1525 (m), 1440 (m); and 1400-1000 cm^{-1} (s), ν (C-F). Its GC/MS and IR spectrum suggested that it is a mixture of acylated diaminodiphenyldisulfide, the benzothiazole, Vf, and its precursor, 2-acylaminobenzenethiol, though under the conditions used for gas chromatographic separation, this thiol was not detected due to its ready cyclization.

Heating the crude product at 110°C for 4 h led to conversion of the precursor to the benzothiazole which did not sublime. But it could be readily extracted preferentially with petroleum ether (40-60°C). This was passed through an alumina column to obtain 2.6 g (yield 67%) of pure Vf as white flaky crystals. Its IR spectrum showed absorptions at 3080 (vw), ν (Ar-H); 1508 (m), 1465 (m), ring stretch; and 1400-1000 cm^{-1} (s), ν (C-F). There were no absorptions due to -NH or -C=O groups.

Preparation of 2-(perfluoro-n-heptyl) benzothiazole(Vc) [8]

Same procedure as above was used to obtain the crude product which was a mixture of benzothiazole and its precursor and disulfides. Its GC/MS showed only one peak identified as the benzothiazole (Vc), although this product melted in a wide range. The IR spectrum showed absorptions at 3340 (m), ν (N-H); 3070 (w), ν (Ar-H); 2630 (w), 2580 (w), ν (S-H); 1730 (s), 1710 (s), ν (C=O); 1610 (w), 1580 (m), 1530 (m), 1480 (w), 1440 (m); and 1400-1000 cm^{-1} (s), ν (C-F).

Heating this product mixture at 100°C under vacuum resulted in the sublimation of Vc as white crystals. Its IR spectrum had absorptions at 3035 (w), ν (Ar-H); 1505 (m), 1460 (m), ring stretch; and 1400-1000 cm^{-1} (s), ν (C-F).

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