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SYNTHESIS OF 2-(PERFLUOROALKYLETER)- AND -(PERFLUOROARYL)
BENZOTHAZOLES⁽¹⁾

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SUMMARY

Benzothiazoles containing 2-perfluoroalkylether as well as perfluoro-aryl substituents have been synthesized by two methods: (1) direct acylation of 2-aminobenzenethiol with perfluoroacyl halides, and (2) the reduction of N,N'-diacyl-2,2'-diaminodiphenyldisulfides followed by dehydrative cyclization. The intermediates formed in the direct acylation procedure are the N-acylaminobenzenethiols rather than the S-acyl derivatives.

INTRODUCTION

2-Perfluoroalkylether benzothiazoles have been synthesized by imide ester condensation [1] as well as lithiation of 2-aminobenzenethiol followed by reaction with acid fluorides [2]. The latter report claims the isolation of S-acyl derivatives as stable intermediates which were cyclized to benzothiazoles at about 200°. It appears that the 2-perfluoroarylbenzothiazoles have not thus far been described.

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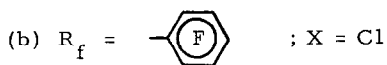
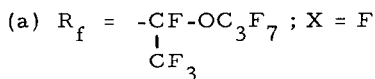
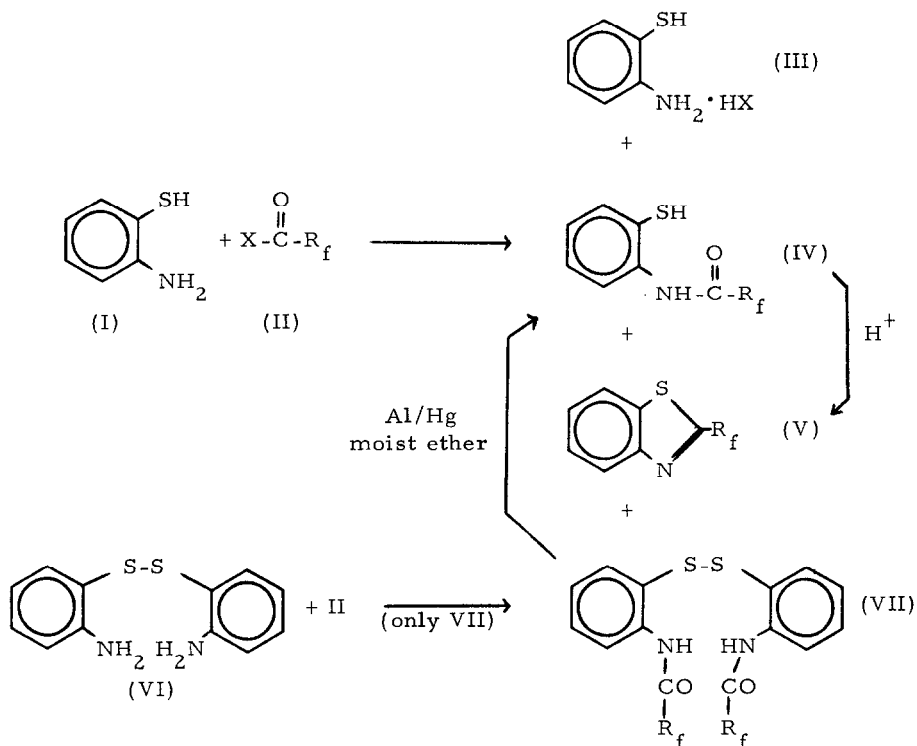
This study is concerned with the preparation of representative compounds from both these classes using readily available acid fluorides. The structure of the intermediates formed were confirmed by synthesizing them by an alternate route.

RESULTS AND DISCUSSION

Direct acylation of 2-aminobenzenethiol (I) (see Illustration) with hexafluoropropene oxide dimer acid fluoride (IIa) at room temperature for four hours gave the N-acyl derivative (IVa) as the major product along with small amounts of the benzothiazole (Va) and the N,N'-diacyldisulfide (VIIa). About 33% of the starting material (I) was converted into the amine salt (IIIa). It was observed that IVa in the crude reaction product was slowly being converted to Va even at room temperature which appeared to be due to the presence of traces of acid in the reaction medium; and as such the intermediate IVa could not be isolated in pure condition from this reaction. The diacyldisulfide (VIIa) was apparently formed by the air oxidation of IVa during isolation of the product. Heating the reaction product at 150-160° completed cyclization of IVa to Va in about four hours in 62% overall yield. Both the acylation and cyclization could be carried out in a single step by conducting the above reaction in refluxing benzene. Under these conditions about 75% yield of the benzothiazole was realized.

Similarly, acylation of I was also carried out with pentafluorobenzoyl chloride in benzene at room temperature to yield 53% of IIb, 42% of IVb and 5% of Vb. The N-acyl derivative (IVb) formed in this case was relatively more stable than IVa and could be isolated and characterized. Conversion of IVb to Vb could be achieved in 78% yield by heating in polyphosphoric acid at 120-140° under N₂ for seven hours. The identity of the N-acyl derivatives produced in these acylations was confirmed by preparing them by an alternate route. The diaminodisulfide (VI) was acylated with II, and the N,N'-diacyl derivatives (VII) formed in 63-97% yield were reduced with Al/Hg in moist ether to give IV in 80-88% yield. Though other reducing agents such as Zn/HCl and Na₂S₂O₄ were tried, they led to multiplicity of products par-

ticularly with VIIb, probably due to the hydrolysis of the amide function in the acidic or basic reduction media used.



Compound IVa could be isolated and characterized only from the neutral reaction medium employed for the Al/Hg reduction and this sample could be preserved without change at about 10^0 under nitrogen for at least one week. On exposure to air at room temperature IVa slowly oxidized, producing about 6% VIIa in seven days. In the presence of added acid, cyclization to the benzothiazole (46% in five days) was the predominant reaction.

It is significant that no S-acyl derivatives were detected in our direct acylations of I. In view of this observation and the reported facile rearrangement of the S-acyl to N-acyl derivatives of I among hydrocarbon analogs [3], the high thermal stability claimed for the S-perfluoroacyl derivatives of I [2] appeared surprising. We, therefore, repeated the reported lithiation of I and reacted it with IIa and IIb. While reaction with IIb gave a complex mixture of products probably due to nucleophilic displacement of the aromatic fluorines, reaction with IIa gave IVa rather than the S-acyl derivative, as verified by comparison with an authentic sample. Attempts to crystallize the crude reaction product, as reported [2], exposed to air, gave VIIa as a crystalline solid melting at 95-97° while IVa had a m.p. of 26-28°.

EXPERIMENTAL

The 2-aminobenzenethiol and the acid halides were distilled and stored under nitrogen before use. All the melting and boiling points are uncorrected. The IR spectra were recorded on Perkin-Elmer model 521 or 621 infrared spectrophotometer as KBr wafer or neat liquids. The NMR spectra were recorded on a Varian XL100 instrument with fluorotrichloromethane and tetramethylsilane, respectively, as internal standards for ^{19}F (94.1 MHz) and ^1H (100.1 MHz) spectra. Chemical shifts are reported as parts per million. The Mass Spectral analysis was performed by chemical ionization technique on a DuPont Model 21-490 mass spectrometer. For GLC analysis, a Hewlett-Packard Model 700 instrument was used, employing stainless steel columns (6' x 1/4" i.d.) packed with either 10% Apiezon L or SE-30 on Chromosorb W. Petroleum ether (36°-54°) was used for recrystallization and TLC analysis.

Acylation of I with IIa

Freshly distilled I (4.2 g; 0.034 mole) dissolved in benzene (25 ml) was stirred under N_2 at room temperature and IIa (11.3 g; 0.034 mole) was added dropwise during 30 mins. The temperature of the reaction mixture increased by about 8° and the contents became turbid. Stirring was contin-

ued for a total of 4 h and the white solid deposited (1.6 g; 32.8%) was filtered off. This was identified as the HF salt of I.

The benzene solution was evaporated in a rotary vacuum evaporator to yield a colorless viscous liquid (14.2 g) which on GLC showed small amounts of VIIa(nc) and an unidentified compound in addition to the major components IVa (nc) and Va in the approximate ratio of 4.5:1. These were identified by spectroscopic and combustion analysis and/or by comparison with authentic samples (see later). Since IVa formed in this reaction was found to cyclize slowly to Va even at room temperature, no attempt was made to separate the components. Instead, the crude reaction mixture was heated at 150-160° in a stream of nitrogen for 4 h whereupon GLC analysis showed almost complete conversion of IVa to Va. The crude reaction product was distilled under reduced pressure giving 9.13 g (62%) of 2-(perfluoro-1-methyl-2-oxapentyl) benzothiazole (Va) (nc) [B.P. 67-69°/4 mm; 230° (Siwoloboff)], mol. wt. obs. M^+ .419; calcd .419; IR: (cm^{-1}): 3060 (Ar C-H); 1550, 1508, 1456, 1428 (benzothiazole ring stretch), 1350-1100 (C-F) and 750 (4 adj. H). No absorptions were observed due to -SH, -NH or -NH₂. ¹⁹F NMR; 79.6 and 82.7 (AB, $J \approx 140$ Hz, OCF₂); 82.0 (t) and 83.0 (m) (both CF₃); 123.0 (OCF, m) and 130.0 (C-CF₂, s). ¹H NMR: 7.6-8.2 (Ph H, m); Analysis: Found: C, 34.46%; H, 0.98%; N, 3.19%. C₁₂F₁₁H₆NO₂S requires C, 34.38%; H, 0.96%; N, 3.34%.

Acylation of I with IIb

I (5.6 g; 0.045 mole) was dissolved in benzene (80 ml) and while being stirred at room temperature in an atmosphere of nitrogen, IIb (10.4 g; 0.045 mole) in benzene (20 ml) was added during 45 min. A white ppt. formed immediately on addition and the temperature of the reaction mixture rose about 5°. Stirring was continued for a total period of 2 h.

The reaction mixture was filtered and the ppt. washed with benzene to yield a white solid (5.5 g). In order to remove any hydrochloride of I formed, this solid was stirred with water and filtered. The water-insoluble residue (1.7 g) melted at 162-165°.

The benzene solution from the above filtration was distilled to remove the solvent and the pale yellow residue obtained was found to be a mixture of IVb (nc), Vb (nc) and unreacted IIb. From this mixture, the latter two components could be extracted with cold petroleum ether. Vb was isolated in about 5% yield. The residue (4.3 g) insoluble in petroleum ether was identical with the solid melting at 162-165° obtained earlier. Hence, the two fractions were combined. Yield, 6.0 g (42%). It was recrystallized from benzene-petroleum ether to yield pure 2-(pentafluorobenzoyl) aminobenzenethiol (IVb) (nc) melting at 165°, mol. wt. obs. M^+ 319; calcd. 319; IR (cm^{-1}): 3260 (N-H), 3100-3000 (Ar C-H), 2540 (S-H), 1660 (C=O) and 755 (1, 2-disubstitution). ^{19}F NMR: 131.0, 143.0 and 152.0 (Ar C-F). ^1H NMR: 2.1 and 2.8 (-NH and -SH; broad), 7.1-7.9 (Ph H, m). Analysis: Found: C, 48.84%; H, 1.96%; N, 4.40%. $\text{C}_{13}\text{H}_6\text{F}_5\text{NOS}$ requires; C, 48.9%; H, 1.9%; N, 4.39%.

Dehydrative Cyclization of IVb

IVb (3.75 g; 0.012 mole) and excess polyphosphoric acid (60.0 g) were placed in a reaction flask fitted with an efficient mechanical stirrer, thermometer and a water condenser. While passing nitrogen through the flask, the contents were vigorously stirred and heated to 120° and maintained at that temperature for 5 h. Effervescence was observed and some white sublimate collected on the cooler parts of the flask. TLC analysis of a hydrolyzed sample on silica, using 1:1 benzene-petroleum ether, showed considerable amount of starting material (R_f 0.35) in addition to the product (R_f 0.72). Hence, the temperature was increased to 140° and the reaction continued for an additional 2 h. At this stage, TLC analysis showed only traces of the starting material.

The reaction mixture was diluted with water and the precipitate filtered and washed repeatedly with water to yield a pale grey solid. This was repeatedly extracted with petroleum ether and the solvent evaporated to yield 2-(pentafluorophenyl) benzothiazole (Vb) (nc). Yield, 2.75 g (78%); m.p. 124-125°. Recrystallization from benzene-petroleum ether gave a sample melting at 125° (sublimes). mol. wt. obs. M^+ 301; calcd. 301; IR (cm^{-1}) No N-H, S-H or C=O absorptions; 3050 (Ar C-H), 1550, 1493,

1460, 1427 (benzothiazole ring stretch) and 760 (1, 2-disubstitution).

^{19}F NMR: 139.0, 151.0 and 161.0 (Ar C-F); ^1H NMR: 7.6-8.2 (Ph H, m).

Analysis: Found: C, 51.8%; H, 1.47%, N, 4.63%. $\text{C}_{13}\text{H}_4\text{F}_5\text{SN}$ requires C, 51.83%; H, 1.34%; N, 4.65%.

Acylation of VI with IIa

To a solution of VI (2.48 g; 0.01 mole) in benzene (50 ml) was added with stirring at room temperature, a solution of IIa (9.96 g; 0.03 mole) in tetrahydrofuran (50 ml) during 15 min. The yellow solution turned green during the exothermic reaction (5° rise). The contents were stirred for 2 h and the solvent evaporated at room temperature to yield a pale green waxy solid. This was stirred with water, and dil. sodium carbonate solution to yield a pale grey solid which on TLC analysis on silica using 1:1 benzene-petroleum ether showed essentially one spot (R_f 0.77). Yield, 8.5 g (97%).

The crude product was recrystallized (3X) from methanol-water to yield N, N'-bis-(perfluoro-2-methyl-3-oxahexanoyl)-2, 2'-diaminodiphenyl-disulfide (VIIa) (nc) as a pale cream solid, melting at 95-97°. mol. wt. obs. M^+ 872; calcd. 872; IR (cm^{-1}): 3270 (N-H), 3100-3000 (Ar C-H), 1710 (C=O), 1350-1100 (C-F) and 743 (1, 2-disubstitution). ^{19}F NMR: 79.8 and 85.3 (AB, $J \cong 142$ Hz, OCF_2); 81.9 (m) and 82.5 (m) (both CF_3); 130.0 (C- CF_2 , s) and 133.0 (OCF, m); ^1H NMR: 7.1-7.6 and 8.4 (Ph H, m) and 9.0 (NH, broad). Analysis: Found: C, 33.16%; H, 1.20%; N, 3.63%; S, 7.37%. $\text{C}_{24}\text{H}_{10}\text{F}_{22}\text{O}_4\text{N}_2\text{S}_2$ requires C, 33.03%; H, 1.15%; N, 3.21%; S, 7.36%.

Acylation of VI with Pentafluorobenzoyl Chloride (IIb)

To a solution of VI (4.96 g; 0.02 mole) in benzene (100 ml) was added with stirring at room temperature a solution of IIb (9.2 g; 0.04 mole) in benzene (20 ml) during 45 min. A pale yellow precipitate started to separate on addition and the temperature of the reaction mixture increased by 5°. The contents were stirred for 3 h and filtered to separate the solid (8.85 g). This solid was stirred with water to remove any hydrochloride formed and

filtered to yield 7.65 g of solid. TLC analysis on silica plate using benzene containing 2% methanol showed a major spot (R_f 0.5) and two minor spots (R_f 0.4 and 0.12), the latter (R_f 0.12) being due to VI. Treatment of the solid with cold methanol gave 4.38 g of a white insoluble solid which showed only the spot with R_f 0.5. This was identical to the white solid (3.7 g) obtained by evaporation of the benzene solution from the above filtration. Total yield, 8.08 g (63%). Recrystallization from benzene-petroleum ether gave white crystals of N, N'-bis(pentafluorobenzoyl)-2,2'-diamino-diphenyldisulfide (VIIb) (nc) melting at 223-224°. mol. wt. obs. M^+ .636; calcd. 636; IR (cm^{-1}) 3365 (free NH), 3255 (bonded N-H), 3100-3000 (Ar H), 1700, 1685 (C=O) and 756 (1, 2-disubstitution); ^{19}F NMR: 141.0, 153.0 and 162.0 (Ar C-F); ^1H NMR: 7.1-7.6 and 7.9 (Ph H, m) and 9.4 (NH, broad); Analysis: Found: C, 48.95%; H, 1.44%; N, 4.35%; $\text{C}_{26}\text{H}_{10}\text{F}_{10}\text{N}_2\text{O}_2\text{S}_2$ requires C, 49.06%; H, 1.57%; N, 4.4%.

A repetition of the above reaction with 3 molar equivalents of IIB did not substantially increase the yield.

Reduction of VII with Aluminum Amalgam in Moist Ether

Al/Hg was prepared as described [4] except that washing with methanol was avoided to prevent any possible formation of MeO^- which could lead to hydrolytic decomposition of the sensitive N-acylaminobenzenethiol formed.

VII (2.0 g) was suspended in dry ether (100-250 ml) and while stirring under an atmosphere of nitrogen, freshly prepared Al/Hg (~2 g) was added in one lot. About 2.0 ml of water was added, few drops at a time. The reaction was followed by GLC or TLC analysis to observe the progress of reduction and formation of any secondary products and was stopped by filtering the residual amalgam. The residue was washed with ether, the combined filtrate dried over anhydrous magnesium sulfate and the ether evaporated under reduced pressure at room temperature to yield the product.

(A) Reduction of VIIb

Reduction was nearly complete in 30 min. beyond which, secondary reaction products were formed, probably by hydrolysis. The white solid obtained was repeatedly extracted with cold petroleum ether to remove small amounts of soluble impurities. Further recrystallization from benzene-petroleum ether produced IVb in 80% yield. m.p. 163-164°. It gave a mol. wt. of 319 by mass spectral analysis and was identical with the sample prepared by acylation of I with IIb. A mixed m.p. determination did not lead to any depression in m.p.

(B) Reduction of VIIa

Reduction was complete at the end of 3 h and the crude product was obtained as a viscous yellow liquid. It was handled as far as possible in an atmosphere of nitrogen. The crude product was dissolved in petroleum ether, filtered to remove a small amount of insoluble impurity and the solvent evaporated at room temperature under reduced pressure. The yellow viscous liquid thus obtained showed only one peak by GLC analysis and on cooling solidified. The solid melted at 26-28°. Yield of 2-(perfluoro-2-methyl-3-oxahexanoyl) aminobenzenethiol (IVa) (nc) was 88%, mol. wt. obs. M^+ 437; calcd, 437; IR (cm^{-1}) 3330 (NH), 3100-3000 (Ar-H), 2540 (SH), 1730 (C=O), 1350-1100 (C-F) and 750 (1, 2-disubstitution). ^{19}F NMR: 80.1 and 84.3 (AB, $J \approx 144$ Hz, OCF_2); 80.8 (t) and 81.6 (m) (both CF_3); 129.0 (C- CF_2 , s) and 131.0 (OCF, dd). ^1H NMR: 3.8 (SH, broad), 7.2-7.6 (Ph-H, m) and 11.3 (NH, broad). Analysis: Found: C, 33.4%; H, 1.41%; N, 3.96%; $\text{C}_{12}\text{H}_6\text{F}_{11}\text{NO}_2\text{S}$ requires C, 32.9%; H, 1.37%; N, 3.2%.

The compound (IVa) was stable at least for one week when kept under nitrogen below 10°, in the absence of any acid.

A sample of IVa left exposed to air at ambient temperature gave at the end of seven days, about 6.0% of VIIa and 0.5% of Va.

Another sample left exposed to air at ambient temperature in presence of <1% HCl showed at the end of five days, 46% of Va and 10% of VIIa.

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