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SYNTHESIS OF 2- AND 2, 5-SUBSTITUTED BENZOXAZOLES AND BENZOTHIAZOLES

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SUMMARY

A number of 2- and 2, 5-perfluoroalkyl and perfluoroalkylether substituted benzoxazoles and benzothiazoles have been prepared. Their relative hydrolytic stability has been examined. In all cases the benzothiazoles were more stable than the benzoxazoles. Substituents in the 2-position offering steric hindrance improve hydrolytic stability.

INTRODUCTION

2-Perfluoroalkyl substituted benzoxazoles and benzothiazoles have been synthesized by a variety of methods [1, 2, 3, 4, 5]. Recently, Burton and Madison [3] in their studies on perfluoroalkyl substituted benzoxazole and benzothiazole polymers have reported an improvement of the original [1] imidate ester condensation reaction by using hexafluoroisopropanol* as the solvent. Our study is concerned with the synthesis of 2- and 2, 5-substituted perfluoroalkyl (R_f) and perfluoroalkylether (R_fOR_f) benzoxazoles and benzothiazoles. The relative hydrolytic stability of these compounds was determined in order to ascertain which structural features tend to improve this property.

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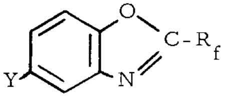
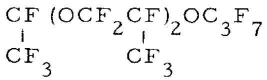
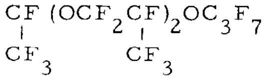
*Hexafluoroisopropanol, $HC(CF_3)_2OH$ is a product of E.I. duPont de Nemours and Company, Wilmington, Delaware, U.S.A.

TABLE 1

Benzoxazoles[a]



R_f	Y	B.P./m.m.	M.S. (found)[b]	Combustion data (calc./found) C	H	N
C_3F_7[c] (X)	H	70°/15	M^+ 287 $(M-19)^+$ 268	41.81/41.56	1.39/1.30	4.88/4.89
C_3F_7 (XI) (nc)	C_3F_7	96°/8	M^+ 455 $(M-19)^+$ 436	34.28/34.40	0.66/0.53	3.08/3.09
$CF_2O(CF_2)_2OC_2F_5$ (XII) (nc)	H	76°/8	M^+ 419 $(M-19)^+$ 400	34.38/34.36	0.96/1.10	3.34/3.32
 $\underset{CF_3}{CF}(OCF_2\underset{CF_3}{CF})_2OC_3F_7$ (IX) (nc)	H	72°/0.07	M^+ 735 $(M-19)^+$ 716	29.41/29.08	0.55/0.46	1.91/2.12
 $\underset{CF_3}{CF}(OCF_2\underset{CF_3}{CF})_2OC_3F_7$ (XIII) (nc)	C_3F_7	95°/0.03	M^+ 903 $(M-19)^+$ 884	27.92/28.14	0.33/0.66	1.55/1.72

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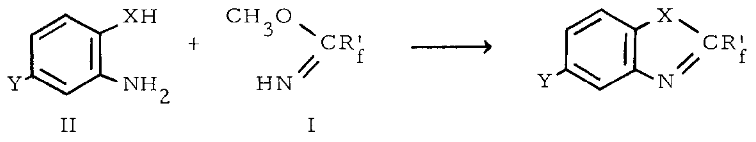
[a] Isolated yields were 70-95%; G.C. yields were ~100% in most preparations; N.M.R. and I.R. data were consistent with structures.

[b] M.S. (mass spectral) analyses were performed by chemical ionization techniques.

[c] Previously reported, ref. 1.

RESULTS AND DISCUSSION

2-Perfluoroalkyl substituted benzoxazoles were originally [1] prepared through the reaction between a perfluoroimidate ester (I, $R_f = CF_3$, C_3F_7) and an ortho aminophenol (II, X = O, Y = H) (equation 1). Utilizing this procedure except with the improvements noted [3] by use of hexafluoroisopropanol we have prepared a number of benzoxazoles and benzothiazoles (see Tables 1 and 2).



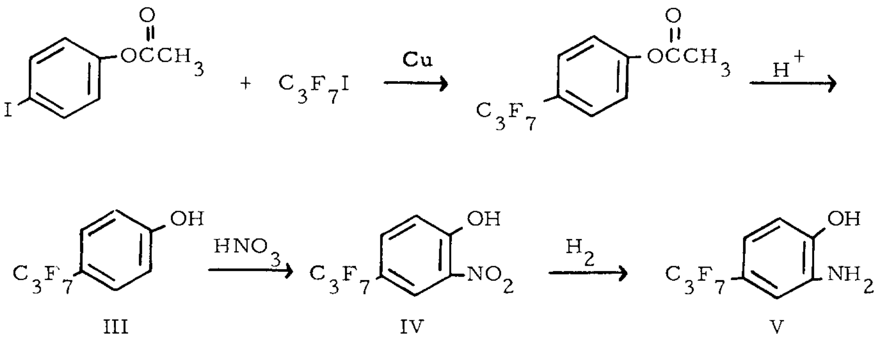
(1)

X = O, S

Y = H (when X = O or S) or C_3F_7 (when X = O)

R_f' = perfluoroalkyl (R_f) or perfluoroalkyleneether (R_fOR_f)

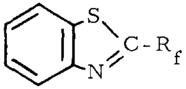
The various imidate esters were prepared through the base catalyzed addition of CH_3OH to $R_f'CN$ [6]. The 2-amino, 4-perfluoropropylphenol (V) was synthesized following a nitration and reduction procedure reported by Evers [7].

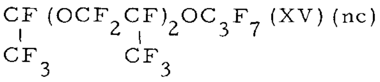


(2)

TABLE 2

Benzothiazoles[a]



R_f	B.P./m.m.	M.S. (found)[b]		Combustion data (calc./found) C	H	N
C_3F_7[c] (VIII)	73°/15	M^+ $(M-19)^+$	303 284	$\frac{39.60}{39.85}$	$\frac{1.32}{1.32}$	$\frac{4.62}{4.76}$
$CF_2O(CF_2)_2OC_2F_5$ (XIV) (nc)	93°/5	M^+ $(M-19)^+$	435 416	$\frac{33.16}{32.85}$	$\frac{0.93}{0.90}$	$\frac{3.22}{3.17}$
 $\underset{CF_3}{CF}(OCF_2\underset{CF_3}{CF})_2OC_3F_7$ (XV) (nc)	85°/0.05	M^+ $(M-19)^+$	751 732	$\frac{28.78}{28.74}$	$\frac{0.54}{0.66}$	$\frac{1.86}{1.95}$

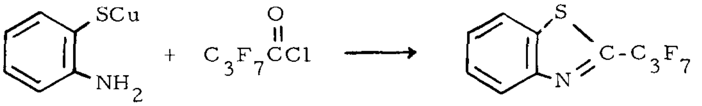
a Isolated yields were 70-89%; N.M.R. and I.R. data were consistent with structures.

b M.S. (mass spectral) analyses were performed by chemical ionization techniques.

c Previously reported, ref. 5.

The rate of the condensation reaction (equation 1) leading to the heterocyclic compounds was conveniently followed by gas chromatographic analysis. Two noteworthy observations were made. The rate of cyclization was decreased with pendent substituents (CF_3) on the alpha carbon of the imidate ester (VI) in the formation of the heterocyclic compounds IX, XIII and XV. This decrease is probably due to a steric hindrance offered by the CF_3 group in the cyclization intermediate step. Secondly, if precautions are not followed to exclude air in the reactions utilizing the 2-aminobenzenethiol, air oxidation of this compound leads to 2,2'-diaminobiphenyldisulfide and a lower yield of the benzothiazole product is observed. In the absence of any such secondary reactions, the cyclization reactions of the benzoxazoles and benzothiazoles appear to be quantitative.

An alternate procedure for the synthesis of a 2-perfluoroalkylbenzothiazole was briefly examined. The S-copper salt of o-aminobenzenethiol (VII) was reacted with perfluorobutyryl chloride in a benzene suspension.* A 58% yield of 2-perfluoropropylbenzothiazole (VIII) was obtained. Although the yields are lower this procedure is more convenient for synthesizing perfluoroalkyl substituted benzothiazoles since it requires readily available perfluoroacyl halides instead of the perfluoroimidate esters.



(3)

VII VIII

Certain heterocyclic compounds substituted with perfluoroalkyl groups have been reported to be hydrolytically unstable [4, 8]. This observation prompted an examination of the relative order of hydrolytic stability of the compounds prepared in this study. A homogeneous solution

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*Jones and Richardson [5] reacted o-$NH_2C_6H_4SLi$ with $C_3F_7C(O)Cl$ and obtained o-$NH_2C_6H_4SC(O)C_3F_7$. Isolation and thermal dehydration of the ester yielded 2-perfluoropropylbenzothiazole.

of the compound was exposed to aqueous, acidic and basic conditions for extended periods of time. The following observations were made on the compounds listed in Tables 1 and 2 under the specific hydrolytic conditions studied (see experimental section).

1. All compounds were stable to H_2O and CH_3COOH hydrolysis.

2. The benzothiazoles were also stable to NH_4OH and HF hydrolysis.

3. The non-branched substituted benzoxazoles (X, XI, XII) were unstable to NH_4OH and HF hydrolysis.

4. The alpha substituted benzoxazoles (IX, XIII) offered increased stability to NH_4OH and HF hydrolysis.

5. Substitution on the benzene ring of the benzoxazole (XI, XIII) increased the rate of hydrolysis by NH_4OH.

Recently [3, 7] some perfluoroalkyl and perfluoroalkyleneether-benzoxazole and benzothiazole polymers have been prepared. The above observations on hydrolytic stability could provide useful guidelines in the solution of perfluoroalkylether substituted heterocyclic compounds or polymers of improved hydrolytic stability.

EXPERIMENTAL

The imidate esters were prepared following the procedure of Brown and Wetzel [6].

Synthesis of $C_3F_7O\,[CF(CF_3)CF_2O]_2\,CF(CF_3)C(=NH)OCH_3$ (VI) (nc)

Approximately 0.1 g of sodium was dissolved in anhydrous CH_3OH (50 ml). To this solution was added $C_3F_7O\,[CF(CF_3)CF_2O]_2CF(CF_3)CN$ (24.6 g, 0.038 mole) and the mixture was stirred at room temperature for 3.5 h. The reaction was then hydrolyzed with water, the lower organic layer was separated and the aqueous layer extracted with CCl_2FCF_2Cl. The extracts and the lower organic layer were combined, dried ($MgSO_4$) and aspirated yielding the crude product (25.6 g).

Distillation yielded the pure imidate ester product (VI) (24.7 g; 96% yield), b.p. 86°/15 mm. Analysis: Found: C, 23.15; H, 0.69; N, 2.24%. $C_{13}H_4F_{23}NO_4$ requires C, 23.13; H, 0.60; N, 2.07%. Mass spectral analysis gave M^+675; calculated M^+675. The infrared and nuclear magnetic resonance spectra were consistent with the imidate ester structure.

By the same procedure as described above, $C_3F_7C(=NH)OCH_3$ (b.p. 74°, 81% yield, ref. [6] reports b.p. 75°, 84%) and $C_2F_5O(CF_2)_2OCF_2C(=NH)OCH_3$(nc) (b.p. 109°, 79% yield) were prepared.

Synthesis of 2-amino-4-perfluoropropylphenol (V) (nc)

A mixture of p-$IC_6H_4OC(O)CH_3$ (19.7 g; 0.075 mole), n-C_3F_7I (33.5 g; 0.113 mole), copper bronze (12.60 g; 0.2 g atom) and dimethylsulfoxide (200 ml) were placed in a glass reactor (Fischer-Porter reactor) bottle and heated with stirring for 5 h in a 125° oil bath. After cooling, the reaction mixture was filtered, hydrolyzed with water, extracted with diethyl ether (3x) and the combined ether extracts were dried ($MgSO_4$) and aspirated yielding a liquid (22 g, 96% yield). Gas chromatographic analysis indicated a single component presumed to be p-$C_3F_7C_6H_4OC(O)CH_3$.

A solution of p-$C_3F_7C_6H_4OC(O)CH_3$ (33.2 g; 0.14 mole) in CH_3OH (200 ml) containing conc. HCl (20 ml) was heated to reflux for 24 h. After cooling and aspiration of the solvent a brown liquid resulted (28.4 g; 99% crude yield). A gas chromatographic analysis indicated primarily one major component. Distillation provided the product p-$C_3F_7C_6H_4OH$ (III) (nc) (26.2 g; 92% yield). Analysis: Found: C, 41.3; H, 1.95%. $C_9H_5F_7O$ requires C, 41.2; H, 1.92%. Mass spectral analysis gave M^+262; calculated M^+262.

A solution of glacial CH_3CO_2H (26 ml) containing conc. HNO_3 (3.6 ml) and p-$C_3F_7C_6H_4OH$ (5.0 g; 0.019 mole) was heated at 37° for 4 h. The reaction was cooled and hydrolyzed with water (200 ml). The mixture was extracted with diethyl ether (3x), the ether fractions dried ($MgSO_4$) and aspirated. Distillation yielded the product 2-nitro, 4-

perfluoropropylphenol (IV) (nc) (4.9 g; 84% yield), b.p. 49°/0.25 mm. Analysis: Found: C, 35.2; H, 1.03; N, 4.56%. $C_9H_4F_7NO_3$ requires C, 35.2; H, 1.31; N, 4.56%. Mass spectral analysis gave M^+307; calculated M^+307.

To a cooled, deoxygenated solution of the above perfluoropropylnitrophenol (33.8 g; 0.11 mole) dissolved in C_2H_5OH (250 ml) was added conc. HCl (25 ml) and platinum on carbon (2 g of a 10% Pt-C). The reactor was flushed with hydrogen and then maintained at a pressure of 50 psi. Shaking of the reactor was maintained for 24 h. The catalyst was filtered and the filtrate aspirated to dryness. The resulting solid was dissolved in water (700 ml), neutralized with $NaHCO_3$ and extracted with diethyl ether and dried ($MgSO_4$). Aspiration of the ether yielded a solid (33.7 g) which on recrystallization from deoxygenated heptane yielded the product 2-amino-4-perfluoropropylphenol (V) (24.3 g; 80% yield), m.p. 116-118°. Analysis: Found: C, 39.1; H, 2.29; N, 5.00%. $C_9H_6F_7NO$ requires C, 39.0; H, 2.18; N, 5.05%. Mass spectral analysis gave M^+277; calculated M^+277. The infrared and nuclear magnetic resonance spectra of all the above intermediates and product were consistent with structures.

Synthesis of 2-$C_3F_7O\,[CF(CF_3)CF_2O]_2CF(CF_3)$-benzoxazole (IX)

A mixture of o-$NH_2C_6H_4OH$ (1.09 g; 0.01 mole), $C_3F_7O[CF(CF_3)CF_2O]_2CF(CF_3)C(=NH)OCH_3$ (VI) (6.75 g; 0.01 mole), glacial CH_3CO_2H (1.14 ml; 0.02 mole) and hexafluoroisopropanol (30 ml) was heated with stirring in an oil bath at 48°. Periodically, a sample was removed and analyzed by gas chromatography. The maximum conversion to the product was attained in five days. The reaction was hydrolyzed with water and the resulting lower organic layer was separated. The aqueous layer was extracted with CCl_2FCF_2Cl and the extracts combined with the lower organic layer and dried ($MgSO_4$). The solvent was removed by aspiration and the remaining material distilled to yield the product (IX) (6.50 g; 88% yield), b.p. 72°/0.07 mm (see Table 1).

All the benzoxazoles and benzothiazoles (see Tables 1 and 2) were prepared by the method described above. The reaction time for maximum yield of product varied with the rate of cyclization. The sterically hindered imidate esters required 5-6 days at 48° whereas some of the non-hindered imidate esters cyclizations were completed within 10 minutes.

Synthesis of 2-n-C_3F_7-benzothiazole (VIII) via o-amino-copperthiophenate

Freshly distilled o-aminothiophenol (73.3 g; 0.59 mole), cuprous oxide (38.0 g; 0.266 mole) and ethyl alcohol (450 ml) were refluxed under nitrogen for 48 h. The reaction mixture was filtered and the residue was washed repeatedly with ethyl alcohol to remove any residual o-aminophenol. The residue was dried in a vacuum oven at 55°. A free flowing light gray material resulted (95 g; 95% yield).

A reaction flask (Fischer-Porter) containing anhydrous C_6H_6 (60 ml), n-$C_3F_7C(O)Cl$ (11.6 g; 0.050 mole) and the o-$NH_2C_6H_4SCu$ (VII) (10.3 g; 0.055 mole) was stirred and heated in an oil bath at 70° for 22 h. After cooling, the mixture was filtered and the filtrate distilled to remove the solvent. A liquid residue (8.5 g; 56% yield) remained which on gas chromatographic analysis indicated one peak. The retention time and an infrared analysis were identical to the product 2-n-C_3F_7-benzothiazole prepared by the imidate ester condensation method (see Table 2).

Hydrolysis of heterocyclic compounds

The simple hydrolytic stability test chosen for this study was not intended to provide precise data for mechanistic interpretations as reported by Jackson et al. [4]. The conditions were chosen in order to observe any hydrolysis in a reasonable time and are accurate to the extent that some generalizations could be inferred.

A weighed sample of the compound (approx. 300 mg) was placed into a 5 or 25 ml glass reaction vial containing anhydrous tetrahydrofuran (2 ml; in the NH_4OH hydrolysis 8 ml was used), and an internal gas chromatographic standard ($C_{12}H_{26}$). To this was added 300 mole % of either H_2O, NH_4OH, CH_3CO_2H or HF. The vial was placed in a constant temperature bath (100° ± 2°) and samples were removed periodically (for one week) and analyzed by gas chromatography. The rate of hydrolysis was determined by the disappearance of the compound in relation to the internal standard. Some of the HF and NH_4OH hydrolysis reactions rates were extremely rapid at 100° and therefore in these instances they were carried out at 22°.

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