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NOVEL PREPARATION OF POLYFLUOROALKYL SECONDARY AND TERTIARY AMINES

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SUMMARY

Primary and secondary amines condense with benzotriazole and a polyfluoroaldehyde to give products which are reduced by sodium borohydride to give the corresponding secondary and tertiary amines containing polyfluoroalkyl groups.

INTRODUCTION

Polyfluoro and perfluoro amines play important roles in medicinal chemistry and biochemistry [1], and in the synthesis of organofluoro compounds. Perfluoro amines have been used in artificial blood substitutes [2]. Polyfluoro amines are useful as fluorinating agents for alcohols, diols and haloalcohols [3]. These facts have stimulated the development of synthetic methods and the search for new applications for this class of compounds.

A variety of methods for the preparation of polyfluoro and perfluoro amines is available including nucleophilic additions of an amine to perfluoro olefines [4] and alkylations of amines by reaction with fluorinated alkyl halides or fluoroalkyl sulfonates [5]. Electrochemical fluorination of secondary and tertiary amines has been used but this yields several by-products arising from incomplete fluorination and from fragmentation reactions [6]. Hydrogenation of nitro groups of fluorinated nitro compounds gave fluorinated amines, and oximes and hydroxyamines as by-products [7]. Fluorinated amines are also accessible by reductions of polyfluoro oximes [8], amides [9] and nitriles [10]. We now describe a new method to synthesize various secondary and tertiary amines containing polyfluoro hydrocarbon groups by the condensation of benzotriazole and a polyfluoroaldehyde

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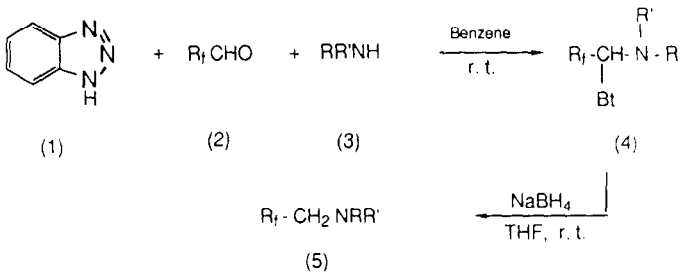
with a primary or a secondary amine, and subsequent reduction with sodium borohydride.

Recent reports from our laboratory have demonstrated the versatile synthetic utility of benzotriazole in the monoalkylation of amines [11], in the alkylation of amides and thioamides, [12] and in the syntheses of amino esters, [13] of N-substituted piperidines [14] and of vicinal diamines [15]. The present paper is the first report of the application of benzotriazole to the synthesis of organofluorine compounds.

RESULTS AND DISCUSSION

Condensations of benzotriazole with aldehydes and primary or secondary amines have been well studied and many benzotriazole derivatives prepared in this way have been used as intermediates in organic syntheses [16]. Reactions of benzotriazole with a polyfluoro- or perfluoro-aldehyde and an amine have, however, not been reported previously. In fact relatively few derivatives of fluoro aldehydes are reported in the literature [17]. Polyfluoroaldehydes differ somewhat in their reactivity from their hydrocarbon analogues [18]: initial carbonyl addition products (for example the hemiacetals) of polyfluoroaldehydes are often quite stable due to the presence of the strong electron-withdrawing polyfluoroalkyl group. It is thus of theoretical, as well as of synthetic, interest to examine condensation of fluoroaldehydes with benzotriazole and amines.

Benzotriazole **1** with polyfluoroaldehydes **2** and primary or secondary amines in benzene at room temperature readily gave the expected condensation products. Thus, polyfluoroalkyl benzotriazole derivatives **4a** to **4h** were prepared in good yields (Scheme 1 and Table 1). However, when diphenylamine was used as the amine component, no Mannich type derivative was obtained and the product was an α-hydroxypolyfluoro-alkylbenzotriazole **6** (Scheme 2) formed by addition of benzotriazole to the carbonyl group of the polyfluoro aldehyde. It was known that primary and secondary amines added readily and exothermically to polyfluoro aldehydes to give either α-hydroxypolyfluoroalkylamines or α,α-diaminopolyfluoroalkanes [19].



(1) (2) (3) (4)

R_f - CH_2 NRR'

(5)

No (4,5)	R_f	R	R
a	$HCF_2CF_2CF_2CF_2$	- $CH_2CH_2CH_2CH_2CH_2$-	
b	$HCF_2CF_2CF_2CF_2$	- $CH_2CH_2OCH_2CH_2$-	
c	$HCF_2CF_2CF_2CF_2$	$C_6H_5CH_2$	H
d	$HCF_2CF_2CF_2CF_2$	p-$CH_3C_6H_4$	H
e	$ClCF_2(CF_2)_4CF_2$	- $CH_2CH_2CH_2CH_2CH_2$-	
f	$CF_3CF_2CF_2OCFCF_3$	- $CH_2CH_2CH_2CH_2CH_2$ -	
g	C_6H_5	$C_6H_5CH_2$	$C_6H_5CH_2$

Bt = Benzotriazol-1-yl

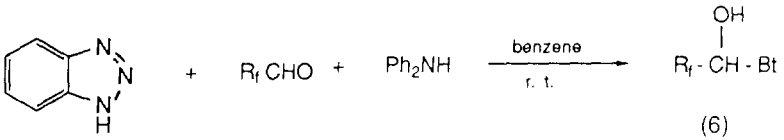
Scheme 1.

TABLE 1

Preparation of Benzotriazole-polyfluoroaldehyde-amine Condensation Products 4 and α-Hydroxyfluoroalkylbenzotriazole 6

No.	yield(%)	m.p.(°C)	Calcd.			Found		
			C	H	N	C	H	N
4a	85	59-60	46.15	3.65	13.46	46.40	3.70	13.37
4b	71	oil	M^+: 418.2934			M^+: 418.2958		
4c	76	51-52	49.31	3.20	12.79	49.14	3.02	13.05
4d	87	95-97	49.31	3.20	12.79	49.21	3.13	12.65
4e	85	100-101	39.24	2.72	10.28	39.38	2.58	10.57
4f	69	>250	40.80	3.00	11.21	41.21	3.21	10.85
4g	100	oil	*					
6a	58	65-67	37.82	2.01	12.03	37.54	2.22	12.68
6b	50	48-50	32.26	1.25	8.69	32.59	1.56	8.38
6c	67	72-74	33.26	1.39	9.70	33.75	1.66	10.01

*. used for further reaction without purification.



(6)

6a : $R_f = HCF_2CF_2CF_2CF_2$
6b : $R_f = ClCF_2(CF_2)_4CF_2$
6c : $Rf = CF_3CF_2CF_2OCFCF_3$

Scheme 2.

The novel benzotriazoles **4** and α-hydroxypolyfluoroalkylbenzotriazole **6** were characterized by elemental analyses (Table 1), and by their ^1H and ^{19}F NMR spectra (see Experimental). The terminal protons in **4a-4d** showed as characteristic triple-triplet signals, and those of the methine CH appeared as multiplets or triple-triplets coupled to fluorine. In the ^{19}F NMR spectra, the AB pattern of the CF_2 adjacent to the chiral carbon atom is most characteristic. Unlike N-aminoalkylbenzotriazoles which generally exist in solution as mixtures of two isomers (i.e. the 1-benzotriazolyl and 2-benzotriazolyl forms) [20], the N-aminofluoroalkylbenzotriazoles were observed only in the 1-benzotriazolyl form.

The benzotriazole moieties in the products derived from benzotriazole, an aldehyde, and an amine, can generally be replaced by a hydrogen atom by reduction. We now demonstrate that polyfluoro derivatives **4**, are reduced to the corresponding secondary or tertiary amines **5** by sodium borohydride in THF at room temperature (Scheme 1). The benzotriazole produced during the reduction is easily removed by extraction into basic aqueous solution. In most cases, the amines produced in this way are essentially pure and the yields are moderate to good, although a polyfluoroenamine, a by-product formed by the elimination of hydrogen fluoride, was detected in a few cases (< 10% based on the ^1H NMR spectra).

The polyfluoroalkyl substituted amines **5** were characterized by elemental analyses and by their ^1H and ^{19}F NMR spectra, especially by a triplet for the CF_2CH_2N protons in the ^1H NMR spectra and the replacement of the AB system of **4** by a triplet for CF_2CH_2N in the ^{19}F NMR spectra (see Experimental).

In summary, a variety of condensation products of benzotriazole, polyfluoroaldehydes and amines were obtained in good yields under mild conditions. Hemiacetals of benzotriazole and polyfluoroaldehyde were produced

when diphenylamine was utilized. The products were subsequently reduced by sodium borohydride to afford secondary and tertiary amines containing polyfluoroalkyl groups. Thus, this sequence provides a general approach to the introduction of a polyfluoroalkyl chain into an amine molecule connected through a methylene group. The particularly mild reaction conditions, simple procedure and good yields offer considerable advantages over previous methods.

EXPERIMENTAL

Melting points were determined with a Thomas-Hoover capillary melting point apparatus and are uncorrected. The ^{1}H and ^{19}F NMR spectra were recorded on JEOL JNM-PMX 60 SI and JEOL JNM FX 90Q instruments. Tetramethylsilane was used as the internal standard for the chemical shift δ in ^{1}H NMR spectra. TFA was the external standard for the ^{19}F NMR spectra. The δ_{CFCl_3} values (positive upfield) were calculated from the equation δ_{TFA} + 77.0 ppm. Elemental analyses were carried out on a Carlo Erba 1106 instrument. Benzene and tetrahydrofuran (THF) were distilled from sodium-benzophenone immediately prior to use. The polyfluoro aldehydes used in this work were purchased from the Shanghai Institute of Organic Chemistry, China.

Condensation of Benzotriazole, a Polyfluoro Aldehyde and a Amine, Typical Procedure

Benzotriazole (20 mmol) and the appropriate amine (20 mmol) were suspended in dry benzene and stirred vigorously for 10 min at room temperature. The polyfluoro aldehyde (20 mmol) was slowly added to the reaction mixture and the stirring was continued for 2-3 h, during which the solid benzotriazole dissolved. The solvent was removed under reduced pressure, and the residue was recrystallized from ethanol or an ethanol-hexane mixture (see Table 1).

1,5-Dihydro-1-(benzotriazol-1-yl)-1-piperidinooctafluoropentane 4a

^{1}H NMR ($CDCl_3$): 8.10-8.30 (m, 1H), 7.35-7.75 (m, 3H), 6.20 (tt, J_{HF}=52Hz, 6Hz, 1H, CF_2H), 6.25 (tt, 1H, $CHCF_2$), 2.90 (m, 4H, 2xNCH_2), 1.75-1.45 (m, 6H, 3xCH_2); ^{19}F NMR: 143.5, 137.3 (AB, J=255Hz, 2F, CF_2CH), 129.7 (d, J_{HF}=8Hz, 2F, CF_2), 123.9 (s, 2F, CF_2), 116.4 (d, J^{2}_{HF}=50Hz, 2F, CF_2H).

1,5-Dihydro-1-(benzotriazol-1-yl)-1-morpholinooctafluoropentane 4b

^{1}H NMR ($CDCl_3$): 8.15-8.30 (m, 1H), 7.40-7.80 (m, 3H), 6.25 (tt, J_{HF}= 52Hz, 6Hz, 1H, CF_2H), 6.30 (tt, 1H, CH), 3.50-3.80 (m, 4H, 2xOCH_2), 2.50-2.80 (m, 4H, 2xNCH_2). ^{19}F NMR: 144.0, 137.1 (AB, J=255Hz, 2F, CF_2CH-), 129.5 (d, 2F, CF_2), 124.1 (s, 2F, CF_2), 116.5 (d, J_{HF}=52Hz, 2F, CF_2H).

1,5-Dihydro-1-(benzotriazol-1-yl)-1-benzylaminooctafluoropentane 4c

^{1}H NMR ($CDCl_3$): 7.70-8.15 (m, 1H), 7.05-7.50 (m, 8H), 6.00 (tt, J_{HF}= 50Hz, 6Hz, 1H, CF_2H), 5.70-6.10(m, 1H, $CHCF_2$), 4.70 (s, 2H, CH_2). ^{19}F NMR: 139.9, 134.8 (AB, J=260Hz, 2F, CF_2CH), 130.5 (m, 2F, CF_2), 124.5 (s, 2F, CF_2), 116.5 (dt, J_{HF}=52Hz, J^4_{FF}=8Hz).

1,5-Dihydro-1-(benzotriazol-1-yl)-1-(4-toludino)octafluoropentane 4d

^{1}H NMR ($CDCl_3$): 8.20-6.85 (m, 8H), 6.05 (tt, 1H, CF_2H), 5.40 (m, 1H, $CHCF_2$), 2.50 (br, 1H, NH), 2.20 (s, 3H, CH_3). ^{19}F NMR: 138.5, 134.5 (AB, J=260Hz, 2F, CF_2CH), 130.8 (m, 2F, CF_2), 124.4 (s, 2F, CF_2), 116.7 (dt, J_{HF}=51Hz, J^4_{FF}=8Hz).

1-Hydro-1-(1-benzotriazol-1-yl)-7-chloro-1-piperidinododecafluoroheptane 4e

^{1}H NMR ($CDCl_3$): 8.05-8.30 (m, 1H), 7.35-7.70 (m, 3H), 5.98-6.40 (m, 1H, CH), 2.75 (m, 4H, NCH_2), 1.70-1.35 (m, 6H). ^{19}F NMR: 144.0, 138.0 (AB, J=280Hz, 2F, CF_2CH), 123.3 (m, 2F), 122.5 (m, 6F), 68.6 (t, J=12Hz, 2F, CF_2Cl).

1-Hydro-1-(benzotriazol-1-yl)-2-heptafluoropropoxy-1-piperidinotetrafluoropropane 4f

^{1}H NMR ($CDCl_3$): 8.10-7.80 (m, 2H), 7.40-7.25 (m, 3H), 3.00 (m, 4H), 1.75-1.40 (m, 6H); ^{19}F NMR: 142.5 (m, 1F, OCFCH), 132.2 (m, 2F, CF_2), 86.0-83.5 (m, 6F, 2CF_3), 82.2 (m, 2F, OCF_2).

1-(1-benzotriazol-1-yl)-1-dibenzylamino-1-pentafluorophenylmethane 4g

^{1}H NMR ($CDCl_3$): 8.00-7.82 (m, 1H, BtH), 7.55-7.20 (m, 13H), 4.42-4.18 (AA'BB', 4H, 2xCH_2).

1,5-Dihydro-1-(benzotriazol-1-yl)octafluoropentan-1-ol 6a

^{1}H NMR ($CDCl_3$): 8.30 (br, 1H, OH), 8.10-7.30 (m, 5H), 6.10 (tt, J = 53 Hz, 7Hz, 1H, CF_2H). ^{19}F NMR: 132.5, 128.4 (AB, J = 285 Hz, 2F, CF_2CH), 129.5 (m, 2F, CF_2), 123.7 (s, 2F, CF_2), 116.4 (d, J_{HF} = 53 Hz, 2F, CF_2H).

1-Hydro-1-(benzotriazol-1-yl)-7-chlorododecafluoroheptan-1-ol 6b

^{1}H NMR ($CDCl_3$): 7.85-7.25 (m, 5H), 4.25 (br, 1H, OH). ^{19}F NMR: 120.6 (s, 2F, CF_2), 120-118 (m, 8F), 68.2 (t, J = 14 Hz, 2F, CF_2Cl).

1-Hydro-1-(benzotriazol-1-yl)-2-heptafluoropropoxytetrafluoropropan-1-ol 6c

^{1}H NMR ($CDCl_3$): 8.15-7.30 (m). ^{19}F NMR: 140.1 (m, 1F, OCFCH), 130.9 (m, 2F, CF_2), 86.2-84.0 (m, 6F, 2xCF_3), 82.0 (m, 2F, OCF_2).

Reduction of Benzotriazole Adducts by $NaBH_4$; Typical Procedure

To the adduct **4** (3 mmol) suspended in THF (30 ml) was added sodium borohydride (0.4 g, 10 mmol) in one portion. The reaction mixture was stirred overnight at 20^{0}C. After most of the solvent was removed under reduced pressure, water was added, and the product extracted with ether. The extract was dried with $MgSO_4$. Removal of the solvent gave the expected polyfluoro amines **5**.

1-(1,1,5-Trihydrooctafluoropentyl)piperidine 5a

Oil (65%), Calcd. for $C_{10}H_{13}F_8N$, C, 40.13; H, 4.35; N, 4.68. Found: C, 40.51; H, 4.20; N, 4.37. ^{1}H NMR ($CDCl_3$): 6.10(tt, J = 51 Hz, 6Hz, 1H, CF_2H), 2.99 (tt, J = 14 Hz, 2Hz, 2H, CH_2CF_2), 2.63 (m, 4H, 2xNCH_2), 1.75-1.35 (m, 6H). ^{19}F NMR: 133.0 (t, J_{HF}= 14 Hz, 2F, CF_2CH_2), 129.6 (m, 2F, CF_2), 124.2 (s, 2F, CF_2), 116.0 (dt, J_{HF} = 51 Hz, J^4_{FF} = 8 Hz, 2F, CF_2H).

1-(1,1,5-Trihydrooctafluoropentyl)morpholine 5b

Oil (54%), Calcd for $C_9H_{11}F_8N$: C, 35.88; H, 3.65; N, 4.65. Found: C, 35.51; H, 3.82; N, 4.71. ^{1}H NMR ($CDCl_3$): 6.10 (tt, J = 52 Hz, 6Hz, 1H, CF_2H), 3.05 (tt, J = 14 Hz, 2Hz, 2H, CH_2CF_2), 3.70 (m, 4H, 2xOCH_2), 2.65 (m, 4H, 2xNCH_2). ^{19}F NMR: 133.1 (t, J_{HF} = 14 Hz, 2F, CF_2CH_2), 129.6 (m, 2F, CF_2), 124.3 (s, 2F, CF_2), 115.7 (dt, J_{HF} = 51Hz, J^4_{FF} = 8Hz, 2F, CF_2H).

N-Benzyl-1,1,5-trihydrooctafluoropentylamine 5c

Oil (59%), Calcd for $C_{12}H_{11}F_8N$: C, 44.86; H, 3.43; N, 4.36. Found: C, 44.98; H, 3.20; N, 3.97. ^{1}H NMR ($CDCl_3$): ($CDCl_3$) 7.70 (br, 1H, NH), 7.30 (s, 5H, C_6H_5), 6.00 (tt, J = 52 Hz, 6Hz, 1H, CF_2H), 3.80 (s, 2H, CH_2), 3.20 (t, J = 16 Hz, 2H, CH_2CF_2).

N-(p-Tolyl)-1,1,5-Trihydrooctafluoropentylamine 5d

Oil (70%), Calcd for $C_{12}H_{11}F_8N$: C, 44.86; H, 3.43; N, 4.36. Found: C, 44.59; H, 3.21; N, 4.59. ^1H NMR ($CDCl_3$): 7.03 (d, 2H), 6.50 (d, 2H), 5.97 (t, J = 53 Hz, 6Hz, 1H, CF_2H), 3.70 (t, J = 15 Hz, CH_2CF_2), 2.20 (s, 3H, CH_3).

1-(1,1-Dihydro-7-chlorododecafluoroheptyl)piperidine 5e

Oil (63%), Calcd for $C_{12}H_{12}ClF_{12}N$: C, 33.22; H, 2.77; N, 3.23. Found: C, 33.61; H, 2.98; N, 2.92. ^1H NMR ($CDCl_3$): 3.22 (t, J = 15 Hz, 2H, CH_2CF_2), 2.65 (m, 4H, 2xNCH_2), 1.80-1.40 (m, 6H, 3xCH_2). ^{19}F NMR: 134.0 (t, J_{HF} = 15 Hz, 2F, CF_2CH_2), 121.0 (s, 2F, CF_2), 120-119 (m, 8F), 68.5 (t, J = 14 Hz, 2F, CF_2Cl).

1,1-Dihydro-1-(1-piperidino)-2-heptafluoropropoxytetrafluoropropane 5f

Oil (50%), Calcd for $C_{11}H_{12}F_{11}NO$: C, 34.46; H, 2.61; N, 3.63. Found: C, 34.17; H, 2.82; N, 3.28. ^1H NMR ($CDCl_3$): 3.87 (d, J = 15Hz, 2H, CH_2CF), 2.70 (m, 4H, 2xNCH_2). 1.90-1.45(m, 6H, 3xCH_2). ^{19}F NMR: 144.0 (m, 1F, OCF), 131.8 (m, 2F), 85-82.5 (m, 6F, 2xCF_3), 81.5 (m, 2F).

N,N-Dibenzylpentafluorophenylmethylamine 5g

m.p. 80-81RC (81%), Calcd for $C_{21}H_{16}F_5N$: C, 66.84; H, 4.24; N, 3.71. Found: C, 67.14; H, 4.18; N, 3.68. ^1H NMR ($CDCl_3$): 7.38-7.20 (m, 10H), 3.71 (s, 2H, $CH_2C_6F_5$), 3.57 (s, 4H, $CH_2C_6H_5$); ^{13}C NMR: 58.5 ($\underline{CH_2}C_6F_5$), 45.6 ($\underline{CH_2}C_6H_5$).

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