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A novel synthesis of 2-per(poly)fluoroalkyl-1H-benzimidazoles or 2-per(poly) fluoroalkyl benzothiazoles

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Abstract

A new method for the preparation of 2-per(poly)fluoroalkyl-1*H*-benzimidazoles or 2-per(poly)fluoroalkyl benzothiazoles from reaction of readily available α-per(poly)fluoroalkyl aldehydes with *o*-phenylenediamine or 2-aminobenzenethiol is presented. A possible reaction pathway is suggested.

Keywords: 2-Per(poly)fluoroalkyl-1H-benzimidazoles; 2-Per(poly)fluoroalkyl benzothiazoles; α-Per(poly)fluoroalkyl aldehydes; *o*-Phenylenediamine; 2-Aminobenzenethiol

1. Introduction

2-Per(poly)fluroalkyl-1*H*-benzimidazoles or 2-per(poly)-fluoroalkyl benzothazoles not only posses high bioactivity [1–3], but also serve as important synthetic intermediates. Various methods have been introduced for the synthesis of such compounds. 2-Per(poly)fluoroalkyl-1*H*-benzimidazoles were prepared by photochemical reaction of R_fI with 1*H*-benzimidazole and a mixture of various R_f substituted products was obtained [4], other methods generally used include condensation of an *o*-diamine with a carboxylic acid [5], reduction of an *N*-(*o*-nitropheynyl)perfluoroalkanamide with concomitant cyclisation of the *o*-amino-derivative [5] and cyclocondensation of phenylenediamine with R_fCOOH in the presence of catalyst [6]. 2-Per(poly)fluoroalkyl benzothiazoles were prepared by the reaction of 2-aminobenzenethiol with fluorinated β-diketones [7] or with β-chloro-α-(trifluoromethyl)acrolein [8].

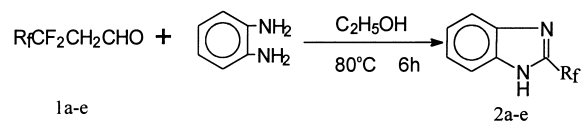
2. Results and discussion

In our continuing study of fluoroalkyl-containing heterocylic compounds, it was found that the reaction of *o*-phenylenediamine with the α-per(poly)fluoroalkyl aldehydes [9,10] could give 2-per(poly)fluoroalkyl-1*H*-benzimidazoles in moderate yield (Scheme 1). The results are shown in Table 1.

The length of the per(poly)fluoroalkyl chain and the presence of ω-bromine showed little effect on the reaction and all the substrates afforded product 2 in nearly the same yield.

Solvent has little effect on the reaction; when other solvents such as acetonitrile, 1,4-dioxane, THF or acetic acid were used, they all gave similar results.

In order to enlarge the scope of the reaction, 2-aminobenzenethiol was used to react with α-per(poly)fluoroalkyl aldehydes. The expected 2-per(poly)fluoroalkyl benzothia-



1a-e 2a-e

Scheme 1.

Table 1
Reaction of *o*-pheynlenediamine with α-per(poly)fluoroalkyl aldehydes

Entry	Substrate	R_f	Product	Yield (%)[a]
1	**1a**	CF_3	**2a**	55
2	**1b**	$ClCF_2$	**2b**	53
3	**1c**	$BrCF_2$	**2c**	54
4	**1d**	$Cl(CF_2)_3$	**2d**	60
5	**1e**	$CF_3(CF_2)_4$	**2e**	62

[a] Isolated yield based on α-per(poly)fluoroalkyl aldehydes.

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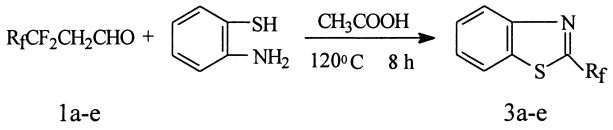


Scheme 2.

Table 2
Reaction of 2-aminobenzenethiol with α-per(poly)fluoroalkyl aldehydes

Entry	Substrate	R_f	Product	Yield[a]
1	**1a**	CF_3	**3a**	48
2	**1b**	CF_2Cl	**3b**	50
3	**1c**	CF_2Br	**3c**	46
4	**1d**	$Cl(CF_2)_3$	**3d**	52
5	**1e**	$CF_3(CF_2)_4$	**3e**	53

[a] Isolated yield based on α-per(poly)fluoroalkyl aldehydes.

zoles were obtained (Scheme 2) and the results are listed in Table 2. However, solvent has great influence on this reaction. Acetic acid was the best choice. When other solvents such as ethanol, acetonitrile, 1,4-dioxane or THF were used, they all give complicated results, which is different from the above mentioned.

A possible reaction mechanism is suggested in Scheme 3.

The reaction of 2-aminophenol with α-per(poly)fluoroalkyl aldehydes was quite different from the two above mentioned reaction and will be discussed in later work.

3. Experimental

All melting points were uncorrected. IR spectra were measured with a Shimadzu IR-440 spectrometer. ^{1}H NMR spectra were recorded at 300 and 90 MHz on Bruker AM300 or JEDLFX-90Q. ^{19}F NMR spectra were recorded on an EM-360L spectrometer at 56.4 MHz using TFA as external standard and positive for upfield shifts. Mass and HRMS spectra were taken on a Finnigan GC–MS-4021 spectrometer. Elements analysis were done by the Elemental Analysis Group of SIOC.

A general procedure for the preparation of compounds **2a**–**2e** was as follows:

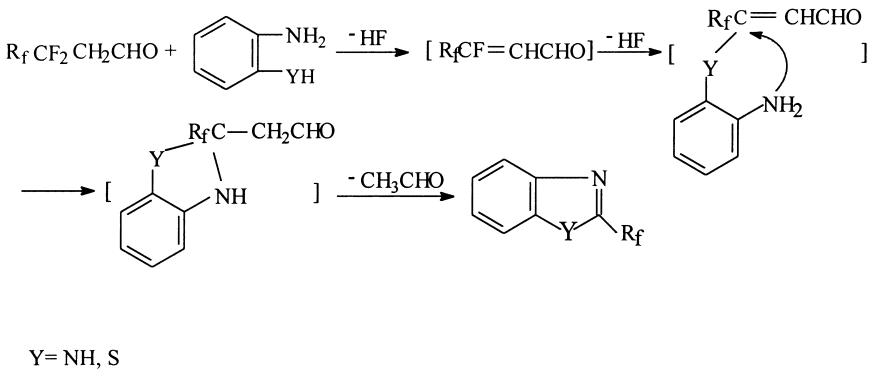
Compound **1** (10 mmol) and *o*-phenylenediamine (20 mmol) were dissolved in 40 ml 95% ethanol. After refluxing at 80°C for 6 h, the mixture was cooled, poured into 50 ml ice water and extracted with diethyl ether (3×40 ml). The organic extracts were combined, washed with brine and dried over Na_2SO_4. The solvent was removed by distillation. The crude product was further purified by silica gel column chromatography, using a mixture of petroleum ether (bp: 60–90°C) and ethyl acetate as eluant (10:1 by volume).

Data for compound **2a**: mp: 210–211°C; ^{19}F NMR (DMSO-d_6) δ −15.7 (s, CF_3); ^{1}H NMR (90 MHz, DMSO-d_6) δ 13.80 (br, NH, 1H), 7.50 (m, 2H), 7.20 (m, 2H); MS (*m/e*) 186 (M^+, 100), 166 (M^+-1-F, 66.45), 116 (M^+-1-CF_3, 19.57); Anal. Calc. for $C_8H_5F_3N_2$: C, 51.62; H, 2.71; N, 15.05; F, 30.62, Found: C, 51.70; H, 2.63; N, 15.12; F, 30.58%.

Compound **2b**: mp: 208–209°C; ^{19}F NMR (DMSO-d_6) δ −28.0 (s, CF_2Cl); ^{1}H NMR (90 MHz, DMSO-d_6) δ 13.80 (br, NH, 1H), 7.50 (m, 2H), 7.20 (m, 2H); MS (*m/e*) 202 (M^+, 40.34), 167 (M^+–Cl, 100); Anal. Calc. for $C_8H_5ClF_2N_2$: C, 47.43; H, 2.49; N, 13.83; F, 18.76, Found: C, 47.50; H, 2.43; N, 13.80; F, 18.83%.

Compound **2c**: mp: 206–208°C; IR: 3400–2500 br, 1592, 1494, 1458, 1442, 1392, 1316, 1282, 1233, 1141; ^{19}F NMR (DMSO-d_6) δ −33.0 (s, CF_2Br); ^{1}H NMR (90 MHz, DMSO-d_6) δ 13.60 (br, NH, 1H) 7.60 (m, 2H), 7.30 (m, 2H); MS (*m/e*) 248 (M^+-1, 29.42), 246 (M^+-1, 25.30), 167 (M^+-1-Br–F, 100); HRMS Calc. for $C_8H_5{}^{79}BrF_2N_2$: 245.9604, Found: 245.9600.

Compound **2d**: mp: 204–206°C; IR: 3400–2500 br, 1593, 1496, 1456, 1440, 1320, 1230, 1182, 1141; ^{19}F NMR (DMSO-d_6) δ −9.5 (s, CF_2Cl), 34.0 (m, CF_2), 44.5 (m, CF_2); ^{1}H NMR (90 MHz, DMSO-d_6; δ 13.80 (br, NH, 1H), 7.70 (m, 2H), 7.30 (m, 2H)) MS (*m/e*): 302 (M^+, 50.32), 267 (M^+–Cl, 14.87), 167 (M^+–C_2F_5Cl, 100); HRMS. Cac. for $^{35}ClC_{10}H_5F_6N_2$; 302.0045, Found: 302.0010; Anal. Calc. For $C_{10}H_5ClF_6N_2$: C, 39.74; H, 1.66; N, 9.27; F, 37.75, Found: C, 39.63; H, 1.32; N, 9.20; F, 37.44%.



Scheme 3.

Compound **2e**: mp: 187–188°C; IR: 3400–2500 br, 1594, 1496, 1456, 1439, 1358, 1318, 1237, 1204, 1144; ^{19}F NMR (DMSO-d_6) δ 3.4 (s, 3F), 33.5 (m, 2F), 45.0 (m, 4F), 49.0 (m, 2F); ^{1}H NMR (90 MHz, DMSO-d_6) δ 13.90 (br, NH, 1H), 7.60 (m, 2H), 7.30 (m, 2H); MS (*m*/*e*): 386 (M^+, 52.02), 367 (M^+–F, 13.85), 167 (M^+–C_4F_9, 100); Anal. Calc. for $C_{12}H_5F_{11}N_2$: C, 37.31; H, 1.30; N, 7.25, F, 54.14, Found: C, 37.52; H, 1.04; N, 7.22; F, 54.33%.

A general procedure for the preparation of compounds **3a–3e** was as follows:

Compound **1** (10 mmol) and 2-aminobenzenethiol (20 mmol) were dissolved in 40 ml acetic acid. After reflexuing at 120°C for 8 h, the mixture was cooled, poured into 50 ml ice water and extracted with diethyl ether (3×40 ml). The organic extracts were combined, washed with saturated $NaHCO_3$ aqueous solution, brine and dried over Na_2SO_4. The solvent was removed by distillation. The crude product was further purified by silica gel column chromatography, using a mixture of petroleum ether (bp: 60–90°C and ethyl acetate as eluant (101 by volume).

Compound **3a**: mp 24–25°C; ^{19}F NMR ($CDCl_3$) δ −15.8 (s, CF_3); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (m, 1H), 8.01 (m, 1H), 7.60 (m, 2H); MS (*m*/*e*) 203 (M^+, 100), 184 (M^+–F, 25.45), 134 (M^+–CF_3, 16.69); Anal. Calc. for $C_8H_4F_3NS$: C, 47.29; H, 1.98; N, 6.89; F, 28.05, Found: C, 47.34; H, 2.01; N, 6.93; F, 27.98%.

Compound **3b**: colorless oil; IR: 1559, 1514, 1459, 1434, 1320, 1284, 1252, 1137, 1122, 1077, 1037, 1015; ^{19}F NMR ($CDCl_3$) δ −29.0 (s, CF_2Cl); ^{1}H NMR (300 MHz $CDCl_3$) δ 8.19 (m, 1H), 7.97 (m, 1H), 7.57 (m, 2H); MS (*m*/*e*) 219 (M^+, 84.77), 184 (M^+–Cl, 100); HRMS Calc. for $^{37}ClC_8H_4F_2NS$: 220.9692, Found: 220.9706.

Compound **3c**: mp: 32–34°C; IR: 1627, 1556, 1503, 1457, 1430, 1322, 1284, 1252, 1168, 1141, 1124, 1079, 1032, 1015; ^{19}F NMR ($CDCl_3$) δ −32.0 (s, CF_2Br); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (m, 1H), 7.95 (m, 1H), 7.56 (m, 2H); MS (*m*/*e*) 265 (M^+H, 25.24), 263 (M^+-1, 20.85), 184 (M^+–Br, 100); HRMS Calc. for $^{79}BrC_8H_4F_2NS$: 262.9216, Found: 262.9194.

Compound **3d**: colorless oil; IR: 3071, 1557, 1512, 1460, 1321, 1296, 1234, 1188, 1126, 1085; ^{19}F NMR ($CDCl_3$) δ −10.5 (s, CF_2Cl), 37.8 (m, CF_2), 42.6 (m, CF_2); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.25 (m, 1H), 8.01 (m, 1H), 7.63 (m, 2H); MS (*m*/*e*) 319 (M^+, 28.79), 284 (M^+–Cl, 9.39), 184 (M^+–C_2F_4Cl, 100); Anal. Calc. for $C_{10}H_4ClF_6NS$: C, 37.56; H, 1.25; N, 4.38; F, 35.68, Found: C, 37.50; H, 1.02; N, 4.42; F, 35.57.

Compound **3e**: mp: 43–44°C; IR: 3070, 1556, 1506, 1457, 1434, 1361, 1323, 1236, 1205, 1138, 1109, 1080, 1049, 1014; ^{19}F NMR ($CDCl_3$) δ 5.0 (s, 3F), 30.0 (m, 2F), 46.0 (m, 4F), 50.3 (m, 2F); ^{1}H NMR ($CDCl_3$) δ 8.23 (m, 1H), 8.01 (m, 1H), 7.60 (m, 2H); MS (*m*/*e*) 403 (M^+, 51.78), 384 (M^+–F, 12.71), 184 (M^+–C_4F_9, 100); Anal. Calc. for $C_{12}H_4F_{11}NS$: C, 35.73; H, 0.99; N, 3.47; F, 51.86, Found: C, 35.86; H, 0.88; N, 3.54; F, 51.82.

Acknowledgements

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