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# Syntheses of Perfluoroalkylated Amines and Diamines by Reactions of Perfluoroalkyl Grignard Reagents with *N*-(α-Aminoalkyl)benzotriazoles

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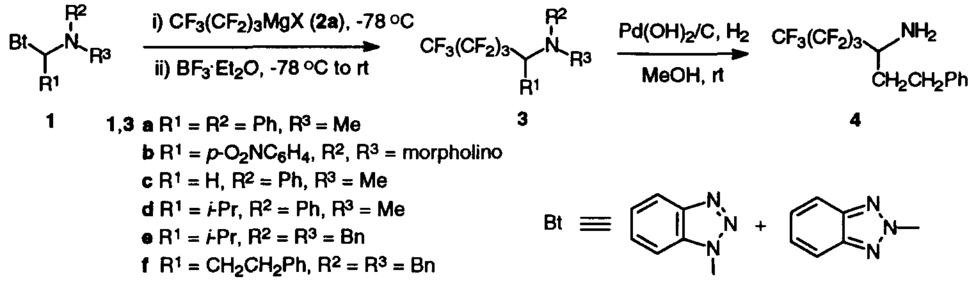
***Abstract:*** The first syntheses of (α,α′-diperfluoroalkylated)diamines are reported together with a range of substituted α-perfluoroalkylated amines all prepared in good yields from benzotriazole derivatives and perfluoroalkyl Grignard reagents in the presence of $BF_3 \cdot Et_2O$. Primary amines are conveniently obtained from Pd-catalyzed hydrogenations. © 1997 Elsevier Science Ltd.

The development of new methodologies to introduce fluorine-containing moieties and the synthesis of fluorine-containing analogs of natural products have attracted much attention due to their potential biological applications.[1,2] Previous syntheses of fluorinated amines are relatively few and include (i) additions of perfluoroalkyllithium to imines,[3,4] by which only secondary amines could be prepared; (ii) Lewis acid catalyzed reductive aminations of trifluoromethylated ketones[5] or base-induced [1,3]-proton shift reactions of fluorinated imines, which required not easily obtained fluorinated ketones or aldehydes;[6] and (iii) use of fluoroalkyl(diethylamido)titanium reagents,[7] which lacks the generality to synthesize different amines. Moreover, none of the aforementioned methods is suitable to prepare bisperfluoroalkylated diamines.

The utility of *N*-(α-aminoalkyl)benzotriazoles as building blocks has been extensively studied within our group.[8,9] The reactions of various Grignard reagents with *N*-(α-aminoalkyl)benzotriazoles have been shown to give easy access to primary, secondary and tertiary amines, and other classes of functionalized amines.[8] However, all of these reactions were performed at room temperature or above, typically in ether or refluxing ether/THF. Therefore, perfluoroalkyl magnesium reagents, which are not stable above -30 °C,[10] could not be used directly. We have now found that perfluoroalkyl magnesium reagents react smoothly with *N*-(α-aminoalkyl)benzotriazoles (**1**) in the presence of $BF_3 \cdot Et_2O$ at -78 °C, to form the corresponding perfluoroalkylated amines **3** in moderate to good yields (Scheme 1, Table 1).

Importantly, many different types of *N*-(α-aminoalkyl)benzotriazoles (which in turn can give rise to many different amines) can be used to prepare various fluorinated amines in 45-73% yields. Ether and nitro functional groups are unaffected in these reactions.



1,3 **a** $R^1 = R^2 = Ph$, $R^3 = Me$
**b** $R^1 = p\text{-}O_2NC_6H_4$, $R^2$, $R^3$ = morpholino
**c** $R^1 = H$, $R^2 = Ph$, $R^3 = Me$
**d** $R^1 = i\text{-}Pr$, $R^2 = Ph$, $R^3 = Me$
**e** $R^1 = i\text{-}Pr$, $R^2 = R^3 = Bn$
**f** $R^1 = CH_2CH_2Ph$, $R^2 = R^3 = Bn$

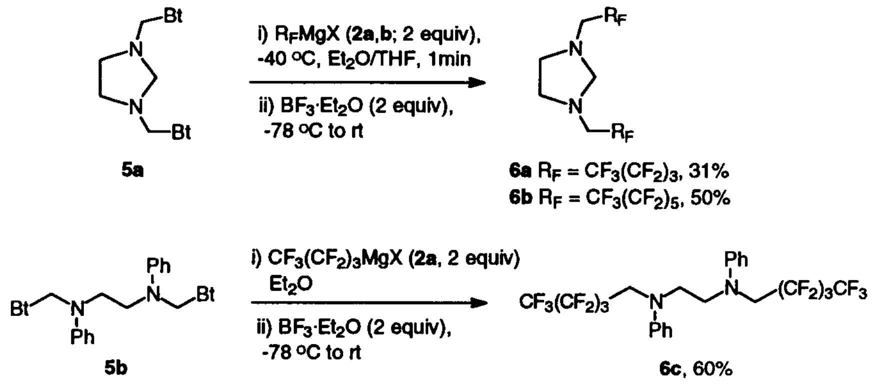
Scheme 1

Table 1. Preparation of Perfluoroalkylated Amines **3** from *N*-(α-Aminoalkyl)benzotriazoles **1**.

| product | $R^1$ | $R^2$ | $R^3$ | isolated yield (%) | CHN found (calcd) C | H | N |
|---|---|---|---|---|---|---|---|
| **3a** | Ph | Ph | Me | 45 | 52.09 | 3.34 | 3.60 |
| | | | | | (52.04 | 3.40 | 3.37) |
| **3b** | $p\text{-}O_2NC_6H_4$ | morpholino | | 61 | 41.28 | 2.91 | 6.58 |
| | | | | | (40.90 | 2.98 | 6.36) |
| **3c** | H | Ph | Me | 73 | 42.25 | 2.82 | 4.01 |
| | | | | | (42.47 | 2.97 | 4.13) |
| **3d** | *i*-Pr | Ph | Me | 60 | 46.90 | 4.23 | 3.84 |
| | | | | | (47.23 | 4.23 | 3.67) |
| **3e** | *i*-Pr | $PhCH_2$ | $PhCH_2$ | 56 | 56.01 | 4.65 | 2.92 |
| | | | | | (56.03 | 4.71 | 2.97) |
| **3f** | $PhCH_2CH_2$ | $PhCH_2$ | $PhCH_2$ | 64 | 60.78 | 4.45 | 2.86 |
| | | | | | (60.77 | 4.54 | 2.63) |

Perfluoroalkylated primary amines can be readily prepared by the removal of the *N*-protecting group of amines **3**. Thus, hydrogenation of fluorinated amine **3f**, using 20% $Pd(OH)_2/C$ as catalyst under 4 kg/cm$^2$ hydrogen pressure in methanol at room temperature for 5 h, gives primary amine **4**, not requiring further purification, in 88% yield.

The present method was extended to the synthesis of (α,α'-diperfluoroalkylated)diamines. Treatment of 1,3-bis(benzotriazol-1-ylmethyl)-1,3-diazolidine (**5a**) or 1,2-bis[*N*-(benzotriazolylmethyl)anilino]ethane (**5b**) with 2 equiv of perfluoroalkyl Grignard reagents afforded bisperfluoroalkylated diamines **6a-c**. Compounds **5** can be easily prepared from the reactions of the corresponding 1,2-ethylenediamine or 1,2-dianilinoethane, benzotriazole and formaldehyde.[11]



Scheme 2

A representative experimental procedure is as follows: Perfluorobutyl Grignard reagent (5 mmol) was first prepared in ether at -78 °C under nitrogen.[12,13] *N*-[(*N*-Methylanilino)benzyl]benzotriazole (**1a**, 4 mmol) was added to the above solution at the same temperature, followed by $BF_3 \cdot Et_2O$ (4 mmol). The reaction mixture was allowed to warm slowly to room temperature overnight, then quenched by the addition of saturated aqueous $NaHCO_3$. After usual extraction and concentration, the crude material was purified by flash column chromatography to give pure amine **3a** in 45% yield.

All of the amines prepared gave satisfactory $^1H$ and $^{19}F$ NMR spectra[14] and microanalysis (C, H, N: ±0.4%). The $^{13}C$ NMR spectra are complicated by long range coupling between fluorine and carbon, and always show many low intensity multiplets (generally 105-125 ppm). However, the carbons $\alpha$ to the nitrogen and perfluoroalkyl group show at around 50-70 ppm a typical triplet or double-doublet, due to the coupling between carbon and fluorine ($^2J$ = 18-28 Hz).

In conclusion, we have developed the reactions of unstable perfluoroalkyl Grignard reagents with *N*-($\alpha$-aminoalkyl)benzotriazoles, and shown their synthetic utility in the synthesis of fluorinated amines and diamines. This approach has led to the first syntheses of bisperfluoroalkylated diamines and supplements previously available methods for fluorinated amines.

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14. Some characteristic analytical data of compounds **3a**, **4** and **6a,c**: *N-Methyl-N-[(1-perfluorobutyl)benzyl] aniline* (**3a**): colorless oil; $\delta_H$ (300 MHz/$CDCl_3$) 2.77 (s, 3H), 5.65 (dd, 1H, $J_{HF}$ = 18.1, 13.6 Hz), 6.84 (t, 1H, $J$ = 7.2 Hz), 6.92 (d, 2H, $J$ = 8.0 Hz), 7.24-7.36 (m, 7H); $\delta_C$ (75 MHz/$CDCl_3$) 33.8, 63.1 (dd, $J_{CF}$ = 25.3, 20.2 Hz), 105.0-124.0 (m, 4C), 114.8, 119.3, 128.6, 129.0, 129.4, 132.2, 149.9; $\delta_F$ (282.2 MHz/$CDCl_3$) -81.4 (t, 3F, $J_{FF}$ = 9.0 Hz), -111.0 and -114.4 (ABm, 2F, $J_{FF}$ = 285.5 Hz), -121.8 and -122.7 (ABm, 2F, $J_{FF}$ = 306.6 Hz), -125.7 and -126.9 (ABm, 2F, $J_{FF}$ = 290.7 Hz). *1-(Perfluorobutyl)-3-phenylpropyl amine* (**4**): yellow oil; $\delta_H$ 1.59 (br, 2H), 1.62-1.72 (m, 1H), 2.07-2.11 (m, 1H), 2.68-2.78 (m, 1H), 2.92-3.01 (m, 1H), 3.22-3.35 (m, 1H), 7.20-7.32 (m, 5H); $\delta_C$ 30.9, 31.7, 52.6 (t, $J_{CF}$ = 22.6 Hz), 105.0-130.0 (m, 4C), 126.2, 128.4, 128.5, 140.8; $\delta_F$ -81.4 (t, 3F, $J_{FF}$ = 9.6 Hz), -122.1 (m, 4F), -126.7 (m, 2F). Anal. Calcd for $C_{13}H_{12}F_9N$: C, 44.18; H, 3.43; N, 3.97. Found: C, 44.20; H, 3.26; N, 4.04. *1,3-Bis[(perfluorobutyl)methyl]imidazolidine* (**6a**): colorless oil; $\delta_H$ 3.00 (s, 4H), 3.23 (t, 4H, $J_{HF}$ = 15.7 Hz), 3.64 (s, 2H); $\delta_C$ 53.8, 54.8 (t, $J_{CF}$ = 23.0 Hz), 78.3, 105.0-125.0 (m, 8C). $\delta_F$ -81.7 (s, 6F), -117.2 (t, 4F, $J$ = 12.7 Hz), -124.7 (s, 4F), -126.7 (s, 4F). Anal. Calcd for $C_{13}H_{10}F_{18}N_2$: C, 29.10; H, 1.88; N, 5.22. Found: C, 29.17; H, 1.67; N, 5.34. *N,N'-Bis[(perfluorobutyl)methyl]-1,2-dianilinoethane* (**6c**): white solid, mp 110-111 °C; $\delta_H$ 3.69 (s, 4H), 3.94 (t, 4H, $J$ = 16.2 Hz), 6.81-6.89 (m, 6H), 7.25-7.31 (m, 4H); $\delta_C$ 49.2, 52.3 (t, $J_{CF}$ = 21.2 Hz), 105.0-125.0 (m, 8C), 113.8, 119.3, 129.5, 147.3; $\delta_F$ -81.5 (t, 6F, $J_{FF}$ = 9.9 Hz), -117.4 (m, 4F), -125.3 (m, 4F), -126.5 (m, 4F). Anal. Calcd for $C_{24}H_{18}F_{18}N$: C, 42.60; H, 2.68; N, 4.14. Found: C, 42.88; H, 2.47; N, 4.02.

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