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Facile synthesis of 1,1-*gem*-dialkylperfluoroalkylamines

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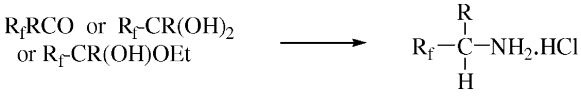
Abstract

Tertiary 1,1-*gem*-dialkylperfluoroalkylamines were prepared by treatment of perfluoroalkylcarboxamides with alkylcerium chlorides, generated from cerium chloride and alkyllithium or alkyl Grignard reagents. The products were easily isolated as the hydrochloride salts. Higher yields were obtained with alkyllithium than with alkyl Grignard reagents.

Keywords: 1,1-*gem*-Dialkylperfluoroalkylamines; Perfluoroalkylcarboxamides; Alkylcerium chlorides; bis-Alkylation

1. Introduction

Fluorine-containing amines play an important role in pharmaceutical and agricultural research due to their unique biological and pharmacological properties (for reviews, see [1–3]). Synthesis of fluoroalkyl-amines has attracted great attention (for reviews, see [2–4]). A practical synthesis of fluoroalkyl- and fluoroaryl-amines has been reported by Soloshonok, et al. [5] through a base-catalyzed [1,3] proton shift reaction from fluoro-containing aldehydes or ketones (or their hydrates). The method is general and efficient to prepare primary and secondary fluoroalkyl- and fluoroaryl-amines in which the carbon adjacent to the amine (C-1) has one or two hydrogens.



We were interested in preparing a series of tertiary 1,1-*gem*-dialkylperfluoroalkylamines in which the C-1 has no hydrogen. The most simple analogue, 2,2,2-trifluoro-1,1-dimethylethylamine, is known in the literature [6,7], prepared in 35% yield by treatment of 2-aminoisobutyric acid with sulfur tetrafluoride in hydrogen fluoride at 120 °C. The reaction conditions are harsh and the reagents corrosive. Furthermore, the method is not generally applicable to synthesis of 1,1-*gem*-dialkylperfluoroalkylamines with other fluoroalkyl groups. Other examples of 1,1-*gem*-dialkylperfluoroalkylamines known in the literature include 2-(perfluorohexyl)-2-aminopropane and 2-(perfluorooctyl)-2-aminopropane, prepared by a radical chain reaction followed by reduction [8], and 1,1-*gem*-diallylperfluorooctylamines, obtained in low yield by reaction of perfluoroalkyl nitriles with triallyltin fluoride [9]. Recent developments in direct nucleophilic trifluoromethylation (for a review, see [10]) with (trifluoromethyl)trimethylsilane ($TMSCF_3$) provide a general approach to various trifluoromethyl-containing amine derivatives, including trifluoromethylaziridines [11], α-trifluoromethylated anilines [12], etc. Now, we report a convenient, general synthesis of 1,1-*gem*-dialkylperfluoroalkylamines by reaction of perfluoroalkylcarboxamides with alkylcerium chlorides. The method is complimentary to the approach reported by Soloshonok, et al. [5] in product structural types.

2. Results and discussion

It was reported that benzamides and thiobenzamides can be dehydrated to benzonitriles and further converted into tertiary carbinamines by treatment with methylcerium chloride generated from cerium chloride and methyllithium [13]. We extended this method to the synthesis of 1,1-*gem*-dialkylperfluoroalkylamines by reaction of perfluoroalkylcarboxamides with alkylcerium chlorides generated from cerium chloride and methyllithium or ethylmagnesium chloride at −78 °C. After completion of the reaction, the mixture was quenched with a small quantity of water. The amine product was obtained together with reaction solvents by distillation. Acidification followed by removal of the

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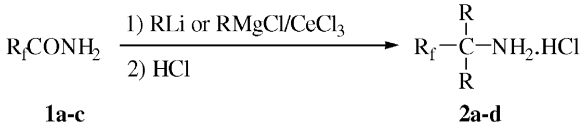
solvents provided the desired 1,1-*gem*-dialkylperfluoroalkylamines as the hydrochloride salts.



1a-c **2a-d**

Entry	R_f	RLi or RMgCl	Yield (%)[a]
a	CF_3	MeLi	80
b	CF_3CF_2	MeLi	67
c	$CF_3CF_2CF_2$	MeLi	62
d	CF_3	EtMgCl	36

[a] Isolated yields.

As shown in the table earlier, good yields were obtained with methylcerium chloride generated from methyllithium (entry **a**–**c**). However, treatment of **1a** with ethylcerium chloride generated from ethylmagnesium chloride provided **2d** in a much lower yield (entry **d**). The lower yield is probably due to low reactivity of Grignard reagents, since a similarly low yield of **2a** was obtained from the reaction of **1a** with methylcerium chloride generated from methylmagnesium chloride.

In conclusion, we have developed a convenient, general synthesis of 1,1-*gem*-dialkylperfluoroalkylamines by reaction of perfluoroalkylcarboxamides with alkylcerium chlorides. Using this method, we have prepared tertiary perfluoroalkylamines that are either unknown in the literature or were previously prepared in lower yield under much harsher conditions. This approach is complimentary to the base-catalyzed [1,3] proton shift reaction [5] in product structural types.

3. Experimental

3.1. General

Melting points were determined in capilaries and not corrected. IR spectra were obtained using a Nicolet-710 FT–IR spectrometer. ^1H, ^{13}C and ^{19}F NMR spectra were recorded with a Bruker Avance 400 spectrometer at 400, 100 and 376.5 MHz, respectively. Chemical shifts are quoted in ppm from internal TMS for ^1H and ^{13}C and from external C_6H_5F (δ, −113.7 ppm) for ^{19}F. Mass spectra were obtained using a Micromass LCT mass spectrometer operating at 20 eV.

3.2. Typical procedure

A suspension of anhydrous $CeCl_3$ (30 mmol) in THF (60 ml) was stirred at room temperature for 1 h. The mixture was cooled to −78 °C, and a solution of methyllithium (30 mmol) in diethyl ether or ethylmagnesium chloride (30 mmol) in THF was added dropwise. The mixture was stirred at −78 °C for 30 min, and a solution of perfluoroalkylcarboxamide (6 mmol) in THF (10 ml) was added dropwise. Stirring was continued at −78 °C for 1 h, and the reaction was gradually warmed to room temperature. Water (0.5 ml) was added, and the mixture was filtered through Celite. The filtrate was transferred to a distillation apparatus. Distillation provided the amine together with reaction solvents (collected in a cold trap). Hydrogen chloride gas was then bubbled through this solution. Removal of the solvents gave the desired 1,1-*gem*-dialkylperfluoroalkylamine as a hydrochloride salt, which was washed with a small amount of hexanes and dried.

3.2.1. 2,2,2-Trifluoro-1,1-dimethylethylamine hydrochloride (**2a**)

White crystals: mp > 200 °C (sublimed). IR (KBr): ν 1053, 1172, 1401, 1533, 1600, 2578, 2800, 2854, 2904 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.66 (s, 6H, CH_3), 9.23 (s, 3H, NH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.0 (s, CH_3), 56.9 (q, J = 26.6 Hz, C-1). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −81.6 (s, 3F, CF_3). MS (electrospray, 20 eV) *m/z*: 128.1 $(M+H)^+$. Anal. calcd. for $C_4H_9ClF_3N$: C, 29.37; H, 5.55; N, 8.56. Found: C, 29.34; H, 5.60; N, 8.69.

3.2.2. 2,2,3,3,3-Pentafluoro-1,1-dimethylpropylamine hydrochloride (**2b**)

Off-white crystals: mp > 200 °C (sublimed). IR (KBr): ν 1013, 1147, 1210, 1529, 2800, 2854, 2926 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.75 (s, 6H, CH_3), 9.29 (s, 3H, NH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.5 (s, CH_3), 57.7 (q, J = 22.4 Hz, C-1), 113.6 (tq, J = 262.2, 37.2 Hz, CF_2), 118.6 (qt, J = 287.2, 35.1 Hz, CF_3). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −79.0 (s, 3F, CF_3), −123.2 (s, 2F, CF_2). MS (electrospray, 20 eV) *m/z*: 178.1 $(M+H)^+$. Anal. calcd. for $C_5H_9ClF_5N$: C, 28.12; H, 4.25; N, 6.56. Found: C, 28.04; H, 4.09; N, 6.70.

3.2.3. 2,2,3,3,4,4,4-Heptafluoro-1,1-dimethylbutylamine hydrochloride (**2c**)

Beige crystals: mp > 200 °C (sublimed). IR (KBr): ν 914, 1121, 1184, 1221, 1591, 2574, 2800, 2942 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.70 (s, 6H, CH_3), 8.93 (s, 3H, NH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.0 (s, CH_3). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −81.2 (t, 3F, J = 11.8 Hz, CF_3), −120.0 (d, 2F, J = 9.2 Hz, CF_2), −123.2 (m, 2F, CF_2). MS (electrospray, 20 eV) *m/z*: 228.1 $(M+H)^+$. Anal. calcd. for $C_6H_9ClF_7N$: C, 27.34; H, 3.44; N, 5.31. Found: C, 27.47; H, 3.40; N, 5.32.

3.2.4. 2-Ethyl-2-(trifluoromethyl)butylamine hydrochloride (**2d**)

White crystals: mp > 200 °C (sublimed). IR (KBr): ν 1152, 1171, 1182, 1205, 1533, 2585, 2880, 2986 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, 6H, J = 7.4 Hz, CH_3), 2.03 (m, 4H, CH_2), 9.26 (s, 3H, NH_3). ^{13}C NMR

(100 MHz, $CDCl_3$): δ 7.3 (s, CH_3), 24.2 (s, CH_2), 62.7 (q, $J = 27.1$ Hz, C-1), 125.1 (q, $J = 284$ Hz, CF_3). ^{19}F NMR (376.5 MHz, $CDCl_3$): δ −75.2 (s, 3F, CF_3). MS (electrospray, 20 eV) m/z: 156.1 $(M + H)^+$. Anal. calcd. for $C_6H_{13}ClF_3N$: C, 37.61; H, 6.84; N, 7.31. Found: C, 37.58; H, 6.65; N, 7.14.

Acknowledgements

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