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Boron Trifluoride-Assisted Reaction of Perfluoroalkyllithiums with Imines. A Novel Route to Perfluoroalkylated Amines

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In the presence of BF_3 , perfluoroalkyllithiums were found to react with imines to give perfluoroalkylated amines in moderate to good yields.

There are the growing interest in organic polyfluoro compounds as building blocks for various potential drug compounds and the subsequent need for methodologies that allow facile incorporation of polyfluoroalkyl moiety into organic molecules. Recently several perfluoroalkylmetallic reagents such as perfluoroalkylzinc, -copper, and -lithium have been introduced for that purpose.^{1,2)} We have also shown that perfluoroalkyllithium can be used for the preparation of perfluoroalkyl carbinols³⁾ and ketones.⁴⁾ This reagent, however, does not react with less reactive electrophiles such as imines, epoxides, and nitriles mainly because of its instability at temperatures above -78 °C. Activation of imines for nucleophilic attack may be achieved by the transformation to immonium salts⁵⁾ or by the complexation with BF₃.⁶⁾ We have now found that perfluoroalkyllithiums add

smoothly to imines <u>1</u> in the presence of BF_3 at -78 °C to give the corresponding perfluoroalkylated amines <u>3</u> in moderate to good yields (Eq. 1).⁷)

The following experimental procedure is representative: To an ethereal solution (50 ml) of N-benzylideneethylamine (<u>1a</u>) (1.33 g, 10 mmol) and perfluorohexyl iodide (<u>2b</u>) (5.35 g, 12 mmol) was added $BF_3 \cdot OEt_2$ (1.3 ml, 10 mmol) and an ethereal solution of MeLi-LiBr (12 mmol) successively at -78 °C. The mixture was stirred for 1 h at this temperature, then quenched by the addition of saturated aqueous NaHCO₃ (30 ml). The organic phase was separated and the aqueous phase was extracted twice with hexane. The combined extracts were washed with brine, dried, and evaporated to yield 4.63 g of the crude material, which was purified by distillation from a Kugelrohr apparatus to give 4.00 g (88%) of pure amine **3b**.⁸)

Perfluoroalkyllithiums derived from straight-chain perfluoroalkyl iodides 2a-<u>d</u> reacted with imines <u>1</u> to give amines <u>3</u> in the yields as shown in Table 1. In contrast, the reactions using branched perfluoroalkyl iodide $\underline{2e}$ gave none of perfluoroalkylation products (entry 5). In these reactions, the complexation of boron trifluoride to imines was essential; imine 1a was recovered unchanged when <u>1a</u> was added to a solution of $C_6F_{1,3}Li$ and BF_3 ·OEt₂, showing that boron trifluoride simply activates the imines by coordination without formation of "ate complexes" with perfluoroalkyllithiums. The bulky group on the imino nitrogen led to diminished yields (entries 6 and 8). Thus, the reaction of N-benzylidene-tbutylamine (1b) with 2b gave amine 3e only in 35% yield under the above given conditions. However, this value was improved to 68% by using 2 equivalents each of $BF_3 \cdot OEt_2$ and $C_6F_{13}Li$ against <u>1b</u> (entry 7). In the case of imine <u>1f</u> (entry 11), the diastereoselectivity attained was as high as that observed in the reaction with allylic boron compounds.⁹⁾ The diastereometric ratio of 3i estimated by ^{19}F -NMR was 25:1. The major isomer was thought to have the erythro geometry (RS and SR) from analogy with the reported results. $^{9,10)}$ On the other hand, the reaction of imine 1g with 2b showed lower diastereoselectivity (1.7:1 determined by 1 H-NMR). It is noteworthy that imine 1a reacts with the perfluoroalkyllithium reagent in preference to methyl benzoate in the presence of BF3.0Et2. Thus, the perfluoroalkylation of an equal molar mixture of 1a and methyl benzoate under competing conditions led to a 7.7:1 mixture of amine $\underline{3b}$ and ketone $\underline{4}$ (estimated by 19 F-NMR). Chromatography of the product mixture gave <u>3b</u> and <u>4</u> in 61% and 7% isolated yields, respectively.

Entr	y Imine <u>1</u>	Perfluor iodid	oalkyl e <u>2</u>	Product		Yield %	Bp θ _b /°C(mmHg ^{a)})
1	PhNEt (<u>1a</u>)	n-C ₈ F ₁₇ I	(<u>2a</u>)	$Ph \rightarrow NHEt C_8F_{17}$	(<u>3a</u>)	79	82-84(0.08)
2	<u>1a</u>	n-C ₆ F ₁₃ I	(<u>2b</u>)	Ph NHEt	(<u>3b</u>)	88	66-68(0.1)
3	<u>1a</u>	n-C ₄ F ₉ I	(<u>2c</u>)	$Ph \xrightarrow{\text{NHEt}}_{C_4F_9}$	(<u>3c</u>)	80	53-55(0.1)
4	<u>1a</u>	C ₂ F ₅ I	(<u>2d</u>)	Ph NHEt	(<u>3d</u>)	91	94-96(18)
5	<u>1a</u>	i-C ₃ F ₇ I	(<u>2e</u>)	_		_	-
6	Ph_N-t-Bu (1	<u>Ib</u>)	<u>2b</u>	Ph \sim NH-t-Bu C ₆ F ₁₃	(<u>3e</u>)	35	70-72(0.1)
7	<u>1b</u>		<u>2b</u>	<u>3e</u>		68 ^b)	
8	Ph N-c-C ₆ H ₁₁	(<u>1c</u>)	<u>2b</u>	$Ph \xrightarrow{NH-c-C_6H_{11}}_{C_6F_{13}}$	(<u>3f</u>)	69	90-92(0.1)
9	PhyN-n-C8H17 Me	7 (<u>1</u> d)	<u>2b</u>	$\overset{Ph}{\underset{Me}{\leftarrow}} \overset{NH-n-C_8H_{17}}{\underset{C_6F_{13}}{}}$	(<u>3g</u>)	82	116-118(0.08)
10 i-	-Pr N-i-Bu (<u>1</u> Me	<u>e</u>)	<u>2b</u>	i-Pr C ₆ F ₁₃	(<u>3h</u>)	84	62-65(0.2)
11 Pł	OMe	<u>f</u>)	<u>2b</u>	$\stackrel{\text{Ph}}{\longrightarrow} \stackrel{\text{NH-n-Pr}}{\underset{\text{C}_{6}\text{F}_{13}}{\overset{\text{NH-n-Pr}}{\longrightarrow}}}$	(<u>3i</u>) ^{c)}	81	91-93(0.08)
12 Me	e ^{N-n-Pr} (<u>1</u>	<u>g</u>)	<u>2b</u>	$\stackrel{\text{Me}}{\underset{\text{MeO}}{\leftarrow}} \stackrel{\text{NH-n-Pr}}{\underset{\text{C}_6\text{F}_{13}}{\leftarrow}}$	(<u>3j</u>) ^{d)}	46	62-65(0.3)

Table 1. Perfluoroalkylation of Imines

a) Kugelrohr oven temperatures. b) The reaction was carried out in the ratio: $\underline{1b}/BF_3 \cdot OEt_2/\underline{2b}/MeLi-LiBr=1/2/2.2/2.2.$ c) Diastereomer ratio estimated by ${}^{19}F-NMR$ was 25:1. d) Diastereomer ratio determined by ${}^{1}H-NMR$ was 1.7:1. Relative stereochemistry could not be assigned.

$$Ph NEt + PhCO_2Me + C_6F_{13}I \xrightarrow{BF_3 \cdot OEt_2 (1 \text{ mmol})} Ph C_6F_{13} + PhCOC_6F_{13} (2)$$

$$\underline{1a} (1 \text{ mmol}) (1 \text{ mmol}) \underline{2b} (1 \text{ mmol}) \xrightarrow{\underline{2b}} \underbrace{\underline{2b}} (1 \text{ mmol}) \xrightarrow{\underline{2b}} (1 \text{ mmol}) \xrightarrow{\underline{2b}} (1 \text{ mmol}) \xrightarrow{\underline{2b}} (1 \text{ mmol}) \xrightarrow{\underline{2b}} \underbrace{\underline{2b}} (1 \text{ mmol}) \xrightarrow{\underline{2b}} \underbrace{\underline{2b}} (1 \text{ mmol}) \xrightarrow{\underline{2b}} \underbrace{\underline{2b}} \underbrace{2b} \underbrace{$$

Perfluoroalkylated primary amine $\underline{5}$ was obtained in virtually quantitative yield by simply heating $\underline{3e}$ with HCl in AcOH (Eq. 3).

$$\begin{array}{ccc} Ph & & 1 & HCl, AcOH, 110 \ ^{\circ}C & & Ph & H^{2} \\ \hline & & C_{6}F_{13} & & 2 & AHCO_{3} \\ \hline & & 3e & & 5 \end{array}$$

$$(3)$$

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