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

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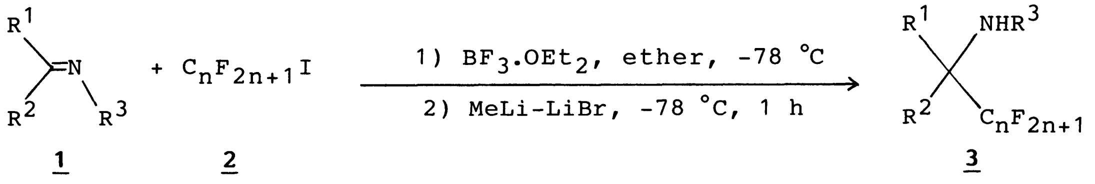
In the presence of BF_3, perfluoroalkyllithiums were found to react with imines to give perfluoroalkylated amines in moderate to good yields.

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 carbinols[3] 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 salts[5] or by the complexation with BF_3.[6] We have now found that perfluoroalkyllithiums add



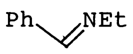
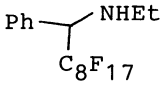
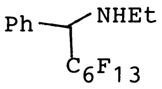
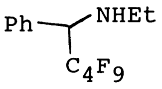
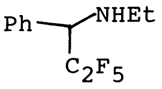
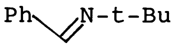
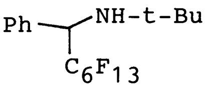
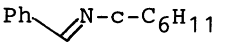
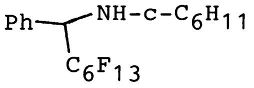
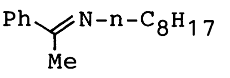
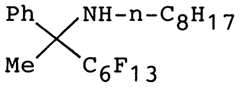
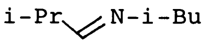
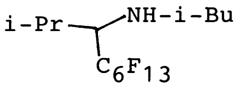
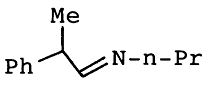
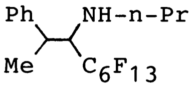
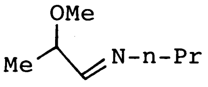
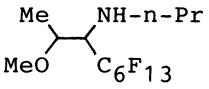
(1)

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

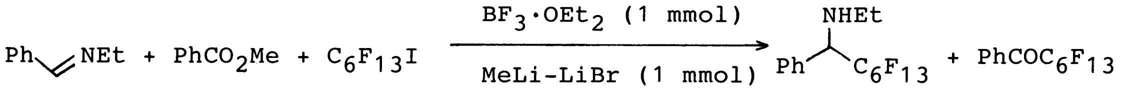
The following experimental procedure is representative: To an ethereal solution (50 ml) of N-benzylideneethylamine (**1a**) (1.33 g, 10 mmol) and perfluorohexyl iodide (**2b**) (5.35 g, 12 mmol) was added $BF_3 \cdot OEt_2$ (1.3 ml, 10 mmol) and an ethereal solution of MeLi-LiBr (12 mmol) successively at -78 °C. The mixture was stirred for 1 h at this temperature, then quenched by the addition of saturated aqueous $NaHCO_3$ (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-d** reacted with imines 1 to give amines 3 in the yields as shown in Table 1. In contrast, the reactions using branched perfluoroalkyl iodide **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 **1a** was added to a solution of $C_6F_{13}Li$ and $BF_3 \cdot OEt_2$, 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-t-butylamine (**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 **1b** (entry 7). In the case of imine **1f** (entry 11), the diastereoselectivity attained was as high as that observed in the reaction with allylic boron compounds.[9)] The diastereomeric 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 ^1H-NMR). It is noteworthy that imine **1a** reacts with the perfluoroalkyllithium reagent in preference to methyl benzoate in the presence of $BF_3 \cdot OEt_2$. 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 **3b** and ketone 4 (estimated by ^{19}F-NMR). Chromatography of the product mixture gave **3b** and 4 in 61% and 7% isolated yields, respectively.

Table 1. Perfluoroalkylation of Imines

Entry	Imine 1	Perfluoroalkyl iodide 2	Product		Yield %	Bp θ_b/°C(mmHg[a])
1	 (1a)	n-$C_8F_{17}I$ (2a)		(3a)	79	82-84(0.08)
2	1a	n-$C_6F_{13}I$ (2b)		(3b)	88	66-68(0.1)
3	1a	n-C_4F_9I (2c)		(3c)	80	53-55(0.1)
4	1a	C_2F_5I (2d)		(3d)	91	94-96(18)
5	1a	i-C_3F_7I (2e)	-		-	-
6	 (1b)	2b		(3e)	35	70-72(0.1)
7	1b	2b	3e		68[b]	
8	 (1c)	2b		(3f)	69	90-92(0.1)
9	 (1d)	2b		(3g)	82	116-118(0.08)
10	 (1e)	2b		(3h)	84	62-65(0.2)
11	 (1f)	2b		(3i)[c]	81	91-93(0.08)
12	 (1g)	2b		(3j)[d]	46	62-65(0.3)

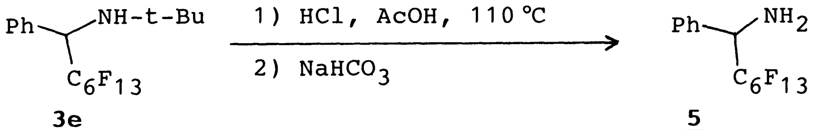
a) Kugelrohr oven temperatures. b) The reaction was carried out in the ratio: 1b/$BF_3 \cdot OEt_2$/2b/MeLi-LiBr=1/2/2.2/2.2. c) Diastereomer ratio estimated by ^{19}F-NMR was 25:1. d) Diastereomer ratio determined by ^1H-NMR was 1.7:1. Relative stereochemistry could not be assigned.



(2)

1a (1 mmol) (1 mmol) 2b (1 mmol) 3b 4 (7.7:1)

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



3e 5 (3)

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8) All new compounds gave satisfactory spectral and analytical data (C, H, N; ±0.4%).

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